UNITED STATES OF AMERICA

+ + + + +

DEPARTMENT OF HEALTH AND HUMAN SERVICES

+ + + + +

FOOD AND DRUG ADMINISTRATION

+ + + + +

CENTER FOR DRUG EVALUATION AND RESEARCH

+ + + + +

NONPRESCRIPTION DRUGS ADVISORY COMMITTEE WITH CONSULTANTS FROM PULMONARY - ALLERGY AND DERMATOLOGIC DRUGS ADVISORY COMMITTEES

+ + + + +

MONDAY
APRIL 22, 2002

+ + + + +

The Advisory Committee met in Versaille Room II in the Holiday Inn, Bethesda, 8120 Wisconsin Avenue, Bethesda, Maryland, at 8:00 a.m., Louis R. Cantilena, Jr., M.D., Ph.D., Chairman, presiding.

PRESENT:
Louis R. Cantilena, Jr., M.D., Ph.D., Chairman
Sandra Titus, Ph.D., Executive Secretary
Leslie Clapp, M.D., Member
Frank F. Davidoff, M.D., Member
Edwin E. Gilliam, Ph.D., Member
Julie A. Johnson, Pharm.D., Member
Edward P. Krenzelok, Pharm.D., Member
Y.W. Francis Lam, Pharm.D., Member
Hari C. Sachs, M.D., Member
Donald L. Uden, Pharm.D., Member

PRESENT: (con't.)

Henry W. Williams, Jr., M.D., Member
Alastair Wood, M.D., Member
Ralph D'Agostino, Ph.D., Nonprescription Drugs SGEs
Mark Dykewicz, M.D., Allergists SGEs
Jesse Joad, M.D., Allergists SGEs
Stan Szefler, M.D., Allergists SGEs
Lloyd King, M.D., Ph.D., Dermatology SGEs
William Rosenberg, M.D., Dermatology SGEs
Michael C. Alfano, D.M.D., Ph.D., Industry Guest

ALSO PRESENT:

Jonca Bull, M.C., FDA
Badrul Chowdhury, M.D., FDA
Charles Ganley, M.D., FDA
Matthew Holman, Ph.D., FDA
Linda Katz, M.D., FDA
Sandy Kweder, M.D., FDA
Charles Lee, FDA
Robert Temple, M.D., FDA
Jonathan Wilkin, M.D., FDA
John Clayton, Ph.D., Schering-Plough
Eugene W. Monroe, M.D. Schering-Plough
Stephen Neuman, Schering-Plough
Patricia Rohane, Schering-Plough
Janet P. Engle, Pharm.D.
Joseph Ferguson, M.D.
Gary Kay, Ph.D.

A-G-E-N-D-A

I-N-D-E-X (con't.)

P-R-O-C-E-E-D-I-N-G-S

8:04 a.m.

DR. CANTILENA: I'm Doctor Lou Cantilena, head of Clinical Pharmacology at the Uniform Services University and chair of this committee. This is the April 22, 2002 meeting of the Nonprescription Drug Advisory Committee.

What I'd like to do is start with introductions. I just introduced myself and perhaps there's less empty seats on this side of the table so perhaps we can start here and have everyone sort of say who you are and your affiliation with the committee.

DR. ALFANO: My name is Michael Alfano and I'm Dean of the Dental School at New York University College of Dentistry.

DR. DYKEWICZ: I'm Mark Dykewicz. I am Director of the training program in allergy and immunology at St. Louis University School of Medicine.

DR. JOAD: I'm Jesse Joad. I'm a pediatric pulmonologist and allergist at University of California at Davis.

DR. SZEFLER: Stan Szefler at National Jewish Medical and Research Center.

DR. D'AGOSTINO: Ralph D'Agostino from Boston University, biostatistician and consultant to the committee.

DR. KRENZELOK: Good morning. I'm Ed Krenzelok. I'm Director of the Pittsburgh Poison Center and a professor of pharmacy and pediatrics at the University of Pittsburgh.

DR. UDEN: I'm Don Uden, University of Minnesota College of Pharmacy and NDAC member.

DR. JOHNSON: I'm Julie Johnson, Professor of Pharmacy Practice and Medicine at the University of Florida and a member of NDAC.

DR. LAM: I'm Francis Lam from the Department of Pharmacology and Medicine at the University of Texas Health Center in San Antonio. I'm also a member of NDAC.

DR. DAVIDOFF: I'm Frank Davidoff. I'm the editor emeritus of *Annals of Internal Medicine.* I'm an internist, and I'm a member of the committee.

DR. GILLIAM: I'm Eddie Gilliam. I'm a

family nurse practitioner with -- Medical Group in Tucson, Arizona.

DR. TITUS: I'm Sandy Titus. I'm the Executive Secretary and the designated federal official at this meeting.

DR. WOOD: I'm Alastair Wood. I'm Assistant Vice Chancellor at Vanderbilt and I'm also a member of the committee.

DR. WILLIAMS: I'm Henry Williams, Acting Chair of the Community Health and Family Practice at Howard University and a member of NDAC.

DR. CLAPP: I'm Leslie Clapp, pediatrics, Main Pediatrics in Buffalo, New York and clinical associate professor of pediatrics at SUNY Buffalo.

DR. KING: I'm Lloyd King, Chief of Dermatology at Vanderbilt University. I'm a dermatologist.

DR. ROSENBERG: I'm Bill Rosenberg. I'm a dermatologist and Chairman of Dermatology at the University of Tennessee College of Medicine.

DR. CHOWDHURY: I'm Badrul Chowdhury. I am with the U.S. Food and Drug Administration,

Division of Pulmonary and Allergy Drug Products.

DR. GANLEY: I'm Charlie Ganley, Director of the Division of Over-the-Counter Drugs at FDA.

DR. KWEDER: I'm Sandra Kweder. I'm the Director of the Office of Drug Evaluation II at FDA.

DR. CANTILENA: Okay. Thank you, everyone.

We'll now ask Doctor Sandy Titus to read the conflict of interest statement.

DR. TITUS: The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting. Based on the submitted agenda for the meeting and all financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of a conflict of interest at this meeting with the following exceptions.

In accordance with 18 USC 208B3, Doctor Ralph D'Agostino has been granted a waiver for his

role as a member of the Safety Monitoring Committee and his services as a consultant to a Safety Monitoring Committee for a competitor on an unrelated matter. He receives fees of less than $10,001 for each of these activities.

Doctor Stanley Szefler has been granted a waiver under 18 USC 208B3 for his consulting for a firm that has a financial interest in a competitive product. He receives less than $10,001 a year.

In addition, Doctor Harry Sachs has been granted waivers under 18 USC 208B3 and 21 USC 355C4, amendment of Section 505 of the Food and Drug Administration Modernization Act for her ownership of stock in the sponsor and competitors valued between $5,001 to $25,000.

A copy of the waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A30 of the Parklawn Building.

In addition, we would like to disclose that Doctor Michael Alfano is participating at this meeting as an industry guest acting on behalf of

regulated industry. As such, he has reported to the FDA that he has no conflicts of interest in the issues to be discussed at today's meeting.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose products they may wish to comment upon.

Thank you.

DR. CANTILENA: Okay. Thank you, Doctor Titus. We're almost ready for our first break at this point after the conflict of interest statement. But let's instead move to Doctor Charles Ganley who will introduce us to the issues for discussion.

DR. GANLEY: We would just like to thank the members of today's Advisory Committee for taking time from their busy schedules to participate in this

meeting. This committee includes members from the Nonprescription Drugs Advisory Committee, selected members from the Pulmonary Allergy Drugs Advisory Committee and the Dermatologic Ophthalmologic Drugs Advisory Committee and some additional FDA consultants.

It was not quite a year ago when the Nonprescription Drugs Advisory Committee and Pulmonary Allergy Drugs Advisory Committee discussed the merits of taking Loratadine Fexofenadine and Cetirizine from prescription to over-the-counter for allergic rhinitis. Today the committee is asked to discuss the merits of taking Loratadine over-the-counter for treatment of chronic idiopathic urticaria. Unlike allergic rhinitis, the indication chronic idiopathic urticaria, urticaria or hives are not approved for any over-the-counter drug products nor is it included in the antihistamine final monograph.

So it is important for the committee to understand today that the discussion will not only impact the supplemental application submitted by Schering Plough but it will also impact other

antihistamine manufacturers that hope to market their product over-the-counter for urticaria and hives.

That concludes my comments right now.

DR. CANTILENA: Okay. Thank you, Doctor Ganley, and I would now like to introduce Doctor John Clayton from Schering Plough to start the sponsor presentation. Doctor Clayton will then introduce his co-presenters and then I believe we'll close the session.

DR. CLAYTON: Good morning, Doctor Cantilena, members of the Advisory Committee, consultants and FDA colleagues. I'm John Clayton, Senior Vice President, Scientific and Regulatory Affairs for Schering Plough Health Care Products. On behalf of Schering Corporation, we appreciate this opportunity to present a brief overview of the NDE submissions we made to the FDA for the approval of Claritin tablets and syrup for over-the-counter status for the indication of chronic idiopathic urticaria.

The proposed labeling of this indication in consumer terms is that of chronic hives of an unknown source. Discussions with FDA have raised the

possibility of a broader hives indication OTC. The research that we are presenting today has been focused on CIU, the current prescription indication. However, we are open to exploring the broader hives indication, as will be discussed by FDA today.

Specifically, the products for discussion today are Claritin tablets, Claritin syrup, Claritin ready tabs rapidly disintegrating tablets, all in 10 milligram daily doses.

By way of background, as Doctor Ganley mentioned, Loratadine was reviewed by this committee along with the Pulmonary Allergy Advisory Committee on last May 11 for the OTC indication of allergic rhinitis. The majority of the Joint Advisory Committee concluded that Loratadine in 10 milligram daily doses is safe for OTC use in allergic rhinitis.

Therefore, the focus of this meeting today is to consider Loratadine for treating the symptoms of chronic idiopathic urticaria as an OTC indication following an initial physician diagnosis.

Schering's presentation this morning will follow the outline shown here. Following my overview,

Doctor Eugene Monroe, a practicing dermatologist with Advanced Health Care in Milwaukee and Assistant Clinical Professor of Dermatology at Medical College of Wisconsin, will present a brief overview of urticaria including the current standards in the diagnosis and treatment.

Mr. Stephen Neuman of Schering will then present the results of four new studies conducted by Schering which provide strong evidence on the appropriateness of CIU as an OTC indication.

This will be followed by a risk benefit analysis of Claritin OTC for this indication and our conclusions and recommendations. At that point, we'll be pleased to respond to any questions you may have.

In arriving at the conclusion that CIU is an appropriate OTC indication for Loratadine, Schering has completed several analyses and studies. First, we undertook an in-depth review of the condition and the current standards and practices of management. This included medical literature as well as practice parameters. We've also conducted four new studies to evaluate patient and physician habits and practices in

CIU, the ability of consumers to self-recognize recurring episodes of CIU following initial physician diagnosis and a label comprehension study of draft OTC labeling for this indication.

We completed an in-depth review of the safety profile of Claritin from clinical trial data as well as the world-wide marketing experience for both allergic rhinitis and CIU and the broad experience with Claritin OTC for skin allergies. We also reviewed poison center data.

And lastly but importantly, we reviewed these findings with a panel of experts in allergy, dermatology and anaphylaxis to gain their insights and recommendations on the appropriateness of the pero switch. This panel included Doctor Randy Jewel, Doctor Ron Simon, Doctor Philip Lieberman, Doctor Richard Aarons, and Doctor Eugene Monroe, who's with us today.

I'd like to summarize the most significant findings from these efforts. First, we learned that CIU is a medical condition that is generally not associated or confused with more serious conditions.

Secondly, we also learned that through the use of OTC antihistamines and/or multiple prescription refills CIU is currently managed as a self-treated condition.

We found that CIU patients and physicians alike are comfortable with consumers' ability to accurately self-recognize recurring outbreaks of CIU which was confirmed through a self-recognition study.

As you will hear from our study results, 62 percent of CIU sufferers surveyed reported they used OTC antihistamines for their hives prior to seeking medical diagnosis. So consumers already self-treat their urticaria symptoms with OTC antihistamines without the benefit of labeling for this use.

And focusing on the drug Loratadine, through an analysis of our adverse event database as well as poison center data, we confirmed that Claritin has an extremely safe record of use and provides a strong risk benefit and we confirmed that adequate labeling can be developed for Claritin for safe and effective use for OTC following an initial physician diagnosis.

I would now like to introduce Doctor

Eugene Monroe. Doctor Monroe is a practicing dermatologist at Advanced Health Care and assistant clinical professor of dermatology at the Medical College of Wisconsin. In addition to his medical practice and teaching, Doctor Monroe has a distinguished research career with numerous publications concerning urticaria. Doctor Monroe.

DR. MONROE: Thank you and I would like to thank the committee for the opportunity to speak before you today. The presentation I'm going to present today has two major objectives. First, I would like to present an overview of urticaria or hives with an emphasis on the classification of this condition, the diagnostic evaluation, and the management of urticaria and secondly, I would like to try to answer the question what, if any, potential consequences could arise if a patient or a consumer misdiagnoses or confuses another condition for chronic idiopathic urticaria.

Urticaria or hives is a skin reaction pattern characterized by transient, pruritic, edematous, lightly erythematous papules or wheals that

frequently have central clearing. To the patient, urticaria is a very itchy bothersome condition and also embarrassing with raised visible wheals. It has a significant negative impact no quality of life affecting the patients' ability to sleep or their daily activities.

Urticaria is basically classified as acute or chronic. Acute urticaria has a duration ranging from a few days to a few weeks. Its incidence is approximately 15 to 20 percent of the general population. The ideology of acute urticaria is usually detectable and most cases are mild and are never seen by the physician.

Chronic urticaria is arbitrarily defined as an episode of urticaria whose duration is greater than six weeks. It can range from a continuous problem occurring almost daily to a recurring problem where there may be symptom-free periods from days to many weeks. The course is variable from months to years. The incidence in the general population is up to three percent.

The etiology of chronic urticaria, unlike

acute urticaria, is not found in 90 to 95 percent of cases and, therefore, most patients with urticaria of a chronic nature have chronic idiopathic urticaria meaning that the cause is unknown or not determined.

The potential causes of urticaria or hives is quite extensive. The most common causes, particularly for acute urticaria, are drugs. Some of the common ones would be the penicillins, the NSAIDs, the anti-hypertensives. Foods are another common cause. This may be the food itself or an additive to the food. Infections that are systemic, -- viral, bacterial, fungal can also underlie urticaria.

There are multiple other causes that are much less frequent as a source, psychogenic factors, physical agents, inhalants, contactants, genetic factors and internal diseases. I would mention under internal diseases that some of the potentially more serious conditions such as connective tissue diseases or vasculitis are probably underlying causes in less than one or two percent of the cases.

In making a diagnosis of chronic idiopathic urticaria, the most important diagnostic

test is a thorough detailed history by the physician. This history would focus on a thorough review of systems and a very thorough review of all the potential causes of urticaria that I listed on the previous slide. A physical examination is also important to detect any underlying problems. Laboratory and diagnostic tests are only ordered based on clues that would be obtained from that thorough history and physical examination. Chronic idiopathic urticaria is a diagnosis of exclusion made by the physician.

I would now like to address the current standards of care for managing urticaria. In cases of acute urticaria, the first critical part of the work-up is to eliminate or reduce an underlying cause since in the vast majority of these cases a cause can be identified.

Patient education is very important. One wants to review with the patient the natural course of the disease and possible ideologies underlying the condition. It is also important to discuss possible complications and associated conditions and what

actions might be appropriate to deal with those situations.

The drug therapy for acute urticaria centers around the use of H1 antihistamines, preferably the non-sedating class.

The management of chronic idiopathic urticaria assumes that an evaluation has already been made by the physician to rule out an underlying etiology. The first step in the management approach would be to reduce or avoid any of the non-specific aggravating factors that often cause vasal dilatation. These would be things like stress, physical exertion, alcohol, exercise, aspirin, etcetera.

Patient education is very important again in alerting the patient to the natural course of the disease and possible underlying etiologies and again the patient should be thoroughly informed of possible complications and appropriate actions to take.

The major maintenance of patients with chronic idiopathic urticaria centers around drug therapy. I would like to briefly summarize what I would consider the treatment algorithm for patients

with chronic idiopathic urticaria.

The standard of care and the first line of therapy is the use of H1 antihistamines with again the non-sedating class being preferred. Sometimes the monotherapy with an H1 antihistamine is insufficient to control the problem and, therefore, other medications are sometimes added for symptomatic relief of the condition. These would include other H1 antihistamines, H2 receptor blockers, inhibitors of other mediators such as leukotriene antagonists or inhibitors of the inflammatory and cellular reaction which is also part of the urticarial reaction.

Urticaria presents a spectrum of patients. The spectrum involves the severity of the condition which ranges from a very mild to a more serious form. Most of the patients with acute urticaria have a mild form of this disease. Most patients with chronic urticaria have a mild to moderate condition and then a small subset have a much more severe refractory condition.

The spectrum of urticaria patients also involves the amount of participation and involvement

and interaction that occurs between the patient and the physician. In acute urticaria, as I stated earlier, most of these patients never even consult with a physician. In chronic urticaria, for the majority of cases that are mild to moderate, patients often self-manage this condition after an initial physician diagnosis and have subsequently infrequent physician contact. The smaller subset of more severe refractory chronic urticaria patients require active physician involvement.

The treatment of the spectrum of urticaria patients centers around the same common theme, the use of H1 antihistamines.

I would now like to turn our attention to the possible question of what would happen in potential situations where a patient or a consumer confuses or misdiagnoses another condition for chronic idiopathic urticaria. What, if any, are the potential consequences if he or she then self-treats the condition with a non-sedating over-the-counter antihistamine? To put these situations in context, it is important to recognize what occurs in today's

health care environment.

I want to focus on those conditions that would most likely be confused or misdiagnosed as chronic idiopathic urticaria. That would include acute or chronic urticaria. It would include the category of eczema and dermatitis such as contact dermatitis and it would include the condition of angioedema. There are other conditions where potential misdiagnosis may occur which are rare or much less frequent such as anaphylaxis, and I'll briefly discuss those later as well.

Let's look first at the condition of acute urticaria. The vast majority of cases of acute urticaria are mild and self-limiting. An appropriate treatment for acute hives is an antihistamine, as I stated earlier. So the conclusion here is that there are no serious clinical concerns or consequences if a person would take an antihistamine for acute urticaria because that's the appropriate thing to do.

Let's look at chronic urticaria. As I stated earlier, approximately five to 10 percent of patients with chronic urticaria have an identifiable

underlying cause. The consequences of confusing chronic urticaria from chronic idiopathic urticaria are that there is a delay in diagnosing the underlying condition which may have alternative treatments. The concern is not serious because these patients will usually be driven to the physician due to the severity and persistence of their itching, the failure of their underlying urticaria to respond to self-treatment, or the presence of other signs and symptoms that might suggest a more serious underlying condition. These might include things such as joint pain, fever, discoloration of the hives, etcetera.

There are many itchy rashes which the consumer might confuse with hives. Some of these would include eczema, contact dermatitis, etcetera. The symptoms of itch in these cases might be helped by the antihistamine but other treatment such as the use of topical cortico-steroids might be required to treat the rash. While the potential for delay in diagnosis and initiation of more appropriate therapy exists, this delay will cause no serious clinical concern or consequence because, again, these patients will

usually seek a physician's care when the symptoms or severity of the condition persists and fails to respond to the treatment initiated.

Angioedema is another condition that I want to briefly mention. Angioedema and urticaria can co-exist approximately 40 percent of the time and sometimes can be confused with each other. Angioedema would be defined as giant hives or hives involving mucous membranes and tissues around the eyes, lips, or genitalia. There is a subset of individuals who can also develop laryngeal or oral angioedema, but this is a very rare situation in chronic urticaria.

Histologically, angioedema involves the deeper layers of the skin than urticaria and very often the angioedema lesions are not pruritic.

Although visually more noticeable than urticaria, angioedema presents no additional serious consequences to the patient if the diagnosis of angioedema is confused with urticaria. In general, there are no differences with the clinical treatment of these conditions which often coexist.

An area of potential concern in the acute

setting relates to the rare situation in which acute urticaria is the presenting symptom of an anaphylactic reaction. Anaphylaxis would be defined as an immediate systemic allergic reaction produced by the release of mediators from the mass cell or the basophil. This would simultaneously involve skin manifestations, hives being present in about 90 percent of these cases, but it would also involve other systemic manifestations. If the respiratory system is involved, one would have dyspnea and wheezing. If the cardiovascular system is involved, dizziness, syncope and hypotension may be present and if the GI system is involved, nausea, vomiting and diarrhea may occur. The incidents of anaphylaxis is rare.

Chronic urticaria is not associated with nor is it a risk factor for the development of anaphylaxis. Acute urticaria is an associated symptom with anaphylaxis but the rapid simultaneous onset of cardiovascular or respiratory symptoms will cause the patient to seek immediate medical attention. The respiratory and cardiovascular symptoms most always

occur within 30 minutes of the presentation of the hives.

I'd like to make the following conclusions. The cardinal features of urticaria, whether acute or chronic, are cutaneous wheals, redness and itching. The diagnosis of chronic idiopathic urticaria is a diagnosis of exclusion made by the physician. The consequences of patient misdiagnosis represents a very low safety risk.

The availability of an over-the-counter non-sedating H1 antihistamine in chronic idiopathic urticaria would represent a significant benefit to the patient or consumer in two ways. It would provide better safety than exists with the current over-the-counter antihistamines and it would create an opportunity for better care through labeling and patient education.

Thank you and at this time I would like to introduce Mr. Stephen Neuman who will present the findings of the Schering chronic idiopathic urticaria studies.

MR. NEUMAN: Thank you, Doctor Monroe.

Good morning, Doctor Cantilena and members of the committee. My name is Steve Neuman and I'm here today to present the results of four studies that we conducted to better understand both patient and physician habits and practices around CIU.

We sponsored four studies on CIU. Many of these were standard studies which would be used to support the switch of a drug of this safety profile. The first was a study among 388 patients who have received a prior physician diagnosis for CIU. The goals of this study were to really understand the fundamental dynamics of the condition such as duration of suffering, the symptoms that are suffered, patient interaction with their physician, and the modalities and treatment methods that are used to manage the disorder.

We also commissioned a study among a representative physician specialties that treat CIU to understand and practice behaviors and perceptions from a physician viewpoint. We conducted a study to determine if consumers that had been diagnosed by a physician as having CIU can accurately self-recognize

the condition and the symptoms upon recurrence. And finally, we conducted a label comprehension study.

One of the key points that I hope you take away from my presentation this morning is the remarkable consistency and findings from these studies, particularly with regard to the patient's ability to self-recognize CIU upon recurrence of symptoms.

Let's begin with the consumer study. Members of a large Internet panel were sent an email questionnaire to help identify physician-diagnosed CIU sufferers. The question that was posed to them was have you ever been diagnosed by a medical doctor as having chronic or recurrent hives that have no known discernible cause, also known as chronic idiopathic urticaria?

A random sample was drawn from among those who responded to the question, and they were sent an email that asked them to log onto a website where they completed a more detailed questionnaire. Importantly, when they logged on, they were rescreened to have physician-diagnosed CIU.

A concern might exist that these respondents were not actually CIU sufferers and, in fact, FDA has raised that concern in their briefing book to you. This is unlikely, I think, due to the fact that the literature on consumer research supports that most respondents provide accurate responses to survey questions on personal health unless the topic is a sensitive health issue. And also, the study remuneration here had a very nominal $8 - $10 value that would be unlikely to attract false claimants in great numbers. And perhaps as important is that the approach to the subject validation used in this study is consistent with what's used in many label comprehension studies.

The study population here was representative of the random sample that was drawn from the larger CIU pool. The demographic profile of this group was consistent with that which has been reported in the literature with CIU. That is, being female and age 40 to 60. I would also point out that it's consistent with the demographics that are reported in the integrated summary of efficacy section

of the CIU clinical study provided by FDA in their briefing book to the committee.

I'll speak about the design now. The questions that were asked consisted primarily of a variation of closed end or multiple choice type questions. However, subjects could type in responses whenever list did not meet their needs and all of the questions pertaining to important patient behaviors had this option available to them. To further minimize the impact or bias in the presentation of these lists, the items in the list were randomly rotated.

In their briefing book, FDA took issue with the use of closed ended questions in this study and while certainly open ended questions do have a role, the modified closed ended questions used in a study of this type are commonly employed and they offer a number of advantages to us. The first is that they're a good choice when options are limited and responses can be anticipated for questions such as where did the wheals occur, what was the length of suffering, items like that.

They also permit a direct comparison of response from subject to subject. They help address the issue that most respondents will not write elaborate answers, particularly in a self-administered questionnaire. And they avoid issues with having the interviewer not carefully record or misinterpret what the subject is saying and they can avoid the errors that are associated with coding or categorization of responses on the back end as well.

What I'd like to do now is move into the findings of the study. The way I'm going to approach this is for each finding I'm going to show the question that was asked and then I'll report the results as well as draw a conclusion.

The first question that was ask is in a typical year, how many episodes of chronic hives do you experience? Two-thirds, 66 percent of sufferers, experienced three or more outbreaks each year and the mean number of outbreaks for the study population is three. This results in a sufferer base who are experienced, frequent sufferers making CIU a recognizable condition, and this ability to self-

recognize CIU will be confirmed, as I mentioned earlier, in several of the studies that I'm presenting today.

We also asked, please indicate the symptoms you experience when your hives recur. The symptoms of hives are quit discreet with nine in 10 naming itching as a symptom. Hives, wheals, redness, rash also received high level of mentions as key symptoms. There's significant consistency in the symptoms that are described by CIU sufferers and, as Doctor Monroe discussed in his section, the key symptom of itching is quite intense and highly bothersome to patients.

It's also noteworthy that symptoms that could be confused with the most threatening manifestations of anaphylaxis such as breathing problems are rare.

An important question that produced key insights for us was thinking about when the hives appeared prior to seeing a physician, what, if anything, did you do to treat or relieve the condition? The question context here is again prior

to diagnosis of CIU.

While OTC antihistamines in the U.S. are not currently labeled to treat symptoms of CIU, the study subjects often used antihistamines to self-treat hives prior to consulting a physician for diagnosis. Nearly two-thirds, 62 percent of patients who've been diagnosed by a physician as having CIU took an OTC antihistamine for their hives prior to physician diagnosis. I point out also that the use of OTC topicals is also a prevalent first step. So we can conclude from this that self-medication prior to physician diagnosis is common behavior and OTCs are commonly used.

One question that we asked regarding physician contact is, in the past year, how often have you seen a physician for this condition? One-third of patients, 33 percent, have not seen a physician for CIU within the past year and nearly 20 percent have not seen a physician since their initial diagnosis. Thus, many patients are not under the continual care of a physician for CIU.

To understand typical behavior upon

recurrence we asked, when your chronic hives recur, please indicate what you normally do. Over half, 52 percent of the subjects, indicate use of a prescribed medication already on hand. Just over four in 10, 43 percent, use an OTC medication and 20 percent indicate that they call their doctor.

So we see that self-management with both prescription and OTCs are common behavior. Looking at this in more detail, particularly at the 20 percent of subjects who typically don't call or visit their doctor when their hives recur, seven percent do so when their symptoms don't respond and another two percent make contact when more serious symptoms occur.

Hence, we would conclude or to summarize, most physician contact comes about when symptoms don't respond or when more serious symptoms occur.

Another important question for us was now that your condition has been diagnosed by a physician, how easy is it for you to identify this condition when it reappears? Once diagnosed by a physician as having CIU, 80 percent of study subjects felt that it was very easy to identify the condition when it recurs and

94 percent felt that it was very or somewhat easy. No respondents felt that it was difficult to identify the condition upon recurrence.

Finally we asked, what would you do if you experienced other symptoms such as difficulty breathing, fever or trouble swallowing with your hives? Over 95 percent of the study subjects indicate that they would seek medical care or call or visit their physician. Importantly, this response is without the benefit of labeling to direct them to an appropriate action.

In their briefing book, FDA indicated that it's not clear whether those subjects who would call or visit a physician would act with a sense of urgency and suggested that a follow-up question on timing would have been helpful. I think while this question might have clarified the results here, I would draw attention to the finding that 55 percent of respondents indicated that they would seek emergency care which implies immediacy. The agency also pointed this out in their discussion of the studies as well.

So to draw conclusions from the consumer

study. First, consumers appear comfortable that based on the frequency of suffering and the discrete symptoms, recurrent episodes of CIU are easy to recognize. Once diagnosed by a physician, CIU is largely self-managed and most patients are not under continual care.

Importantly, treatment with OTC antihistamines prior to physician diagnosis is common behavior today and consumers know to seek medical attention if serious symptoms occur.

Now I would like to focus our attention on the study that we conducted among physicians who regularly see patients with CIU to help better understand the practices among those physicians. This sample was drawn from a pool of physicians with Internet access, and the pool was comprised of over 200,000 physicians representing over 40 percent of AMA registered physicians.

The panel was pre-screened as to specialty and treatment of patients suffering CIU and a longer, more detailed survey was conducted among the sample of the screened physicians. The sample was

representative of and projectable to the universe of office-based physicians with Internet access, which is 96 percent of the physicians in the specialties that we studied, and the sample reflected the primary CIU treatment groups of PCPs defined here as internists and FP-GPs, dermatologists, allergists and pediatricians which incidentally, according to an independent tracking service of office visits, accounts for 89 percent of the office visits for chronic hives. The ending sample was 359.

The first question we asked physicians, what terminology do you typically use when explaining the initial diagnosis to your patients? Chronic or recurring hives are the most prevalent descriptors used by nearly 75 percent of physicians for CIU. This information was a source of learning that helped us with labeling which we later tested in a label comprehension study and I'll review it with you.

After receiving a diagnosis of chronic idiopathic urticaria from a physician, how likely do you feel that a sufferer is able to self-identify or recognize recurrent episodes of the condition? This

question is very similar to the one that was asked of the consumers. Ninety six percent of the physicians believed that it is either very or somewhat likely that their patients can recognize a recurrence. Six in every 10 physicians believed that it's very likely that a recurrence can be recognized. Again, this level is extremely comparable to that which we saw in a similar question in the consumer study.

Another question was, thinking of all the patients you have counseled for chronic idiopathic urticaria, what percentage do you recommend keep a medicine on hand in anticipation of a recurrent episode? Counseling at least some CIU patients to keep medications on hand in case of outbreak of hives is nearly universal behavior and interestingly, just under 60 percent of physicians counsel all of their previously diagnosed CIU patients to keep medications on hand in case of an outbreak. Hence, the physician behavior encourages self-management.

So what can we conclude from this representative and projectable study among physicians first? Physicians appear aligned in the terminology

they use to describe CIU patients, either chronic hives or recurrent hives. Like the 94 percent of consumers who believe that recurrent episodes of CIU are easily self-recognized, a similar proportion, 96 percent, of physicians believe that once diagnosed, it's likely that patients can self-recognize recurrent outbreaks.

Finally, physician prescribing and recommending behavior reinforces CIU patient self-management.

Now I'd like to direct our attention to a study of consumers' ability to self-recognize the condition of CIU upon recurrence. This study was conducted in conjunction with a label comprehension study. A key focus of the study was to understand whether consumers who have been diagnosed by a physician as having CIU can accurately self-recognize the condition and the symptoms upon recurrence.

The design of this study permitted all comers, that is anyone who believes they've been diagnosed by a physician with CIU, to come forward and to participate. The ending sample was 196 CIU

sufferers. CIU patients were recruited from 21 regionally dispersed cities and the patients were required to bring the name and telephone number of the doctor that diagnosed them. This brings greater credibility to the fact that all the enrollees were CIU sufferers.

The subjects that were enrolled in the study, first of all, had a medical history taken along with a photograph of their lesions if they were suffering and willing to be photographed. The patients who were not suffering or refused photographic consent reviewed alternative textbook type photos of lesions and selected the one that looked the most like theirs.

These materials were then sent to and reviewed by the investigating physician who asked additional questions via teleconference with the patient and then the physician investigator and overseeing dermatologist reviewed all of the information to determine if the subject had accurately self-recognized their condition as CIU. Nearly all, 94 percent, of the subjects who believed they had CIU

actually did have the condition.

So what can we conclude from this? Previously diagnosed CIU patients can accurately self-recognize the symptoms and the condition upon recurrence and this is consistent again with the findings of both the consumer and the physician studies.

We also conducted a label comprehension study. This was an all comer study to understand the consumer's ability to comprehend specific communications points on the draft labeling. There were five cohorts in this study. There was a cohort of 196 CIU sufferers. There was a cohort representative of the general population. There was a cohort of individuals screened to read at a maximum 7th - 8th grade level. There was a cohort of patients for whom the labeling for Claritin was contraindicated. That is, those who were either nursing or breast feeding or had liver or kidney disease. And a cohort of acute hive sufferers who, according to the label, should not use the product. Please note that the number of subjects here in each

cohort does not add up to 565 as subjects count toward more than one cohort.

The study method here was the CIU cohort was recruited via advertising and the other cohorts were recruited via mall intercepts and intercepts at special locations for the enriched populations. Label comprehension was assessed by asking both direct and scenario-based questions and self-selection was assessed by posing a question to determine if consumers understood that they personally could use Claritin.

In response to the scenarios that were presented, consumers in all of the cohorts demonstrated a strong understanding of the general warnings and that Claritin should not be used in situations where serious symptoms are present. Either responses that were correct such as "do not take the product" or those that were acceptable such as "I would ask my doctor before using" were mentioned by between 75 and 96 percent depending on the cohort.

Similarly, there was strong understanding of who can and can not use Claritin. The correct and

acceptable levels here were in the range of 75 to 99 percent.

End of condition such as pregnancy or liver disease under which one must ask a doctor before use. The correct and acceptable levels here are in the range 94 to 100 percent and of conditions under which the product should be used correct and acceptable levels, 95 to 100 percent. These responses, taken with the information from the consumer study, that 95 percent of subjects will seek medical attention if serious symptoms are present supports the perspective that labeling can be developed to adequately convey the warnings and an understanding not to use the product if serious symptoms occur.

Response among the CIU sufferers to the scenarios and to the questions was particularly strong with responses ranging from 91 to 99 percent providing either correct or acceptable responses to these questions and CIU patients also universally demonstrate appropriate self-selection for personal use.

A majority of the acute hives cohort, 54 percent, correctly de-selected the product for personal use. I'd like to note that the principal display panel of the package labeling that we tested stated that Claritin, quote, "relieves and reduces itching and rash due to chronic and recurring hives." Unquote. We believe this inclusion of broader symptom descriptors likely led to more acute hive sufferers believing that the product is for their use.

In response to a separate scenario question that asked, what should be done in a situation in which an outbreak of acute hives has occurred, 75 percent of the acute hives cohort correctly comprehended that the product should not be used. This level of self-selection and comprehension leads us to believe that labeling can be improved.

Turning out attention to the general population, seven in 10 members of the general population cohort provided a correct or an acceptable response, i.e., do not use, ask a doctor before use, to the personal use question. We believe that this level can be strengthened even more with revised

labeling.

So our conclusions. Reaction to the scenarios across the cohorts demonstrates understanding of general warning situations in which Claritin should and should not be used and the directions for us.

Results of the self-selection and personal use question reveal that the majority of the general population can appropriately self-select the product for use.

Over half, 54 percent, of the acute hives cohort indicated that they would not use the product when asked a question about personal use and the response to the scenarios underscores that this study population understands the warnings.

These encouraging results were achieved with draft labeling that would benefit from refinement, and we are committed to work with FDA to refine the labeling and improve comprehension among these consumers.

Based on responses to both the self-selection question and to the scenarios, consumers

with a physician diagnosis of CIU understand that Claritin is appropriate for their use and are likely to use it correctly. These findings are again aligned with what we have learned in the other studies.

I would like to ask Doctor Clayton to return and complete our presentation. Thank you.

DR. CLAYTON: I would now like to turn the focus to risk benefit analysis for Claritin for OTC treatment of CIU. As I mentioned at the outset, the safety of Claritin was reviewed with this committee by FDA last May. FDA's analysis included experience in allergic rhinitis patients as well as CIU patients. This analysis was included in the Schering briefing book that FDA provided to you.

This morning I'd like to highlight the significant additional world-wide marketing experience on Loratadine and CIU and other skin allergies which also supports OTC status. We believe that the risk benefit analysis strongly supports a CIU indication for Claritin OTC which is similar to allergic rhinitis.

As you're well aware, Claritin is not a

new drug. It has enjoyed world-wide marketing experience in just over 14 years since its initial launch in Belgium in 1988. While Claritin has ultimately been approved in a total of 114 countries, it is especially important to today's discussion that it has been approved OTC in some 33 countries including Canada since 1990 and the UK since 1993. It is important also that most of these OTC approvals have included indications beyond chronic idiopathic urticaria including urticaria or skin itching and hives. Hence, our adverse experience database on these products covers even broader use experience than CIU alone.

Claritin has been marketed by prescription for CIU in the U.S. since 1995 following its initial launch for allergic rhinitis in 1993. World-wide patient exposure to Claritin has been substantial totalling approximately 14 billion patients days since its initial commercial launch. Almost half of that exposure has been within the U.S. Based on an average treatment regimen of 30 days, this represents 457 million courses of therapy. With this extensive

patient exposure, we believe we have a clear indication of the safety of this drug. Our analysis of our internal database as well as that of poison control centers shows that Claritin has an excellent safety profile with only two adverse event reports per 100,000 courses of treatment.

Serious adverse events are rare and important to OTC consideration, Claritin is not a drug of abuse. It is also important to note that adverse event experience in CIU has not shown any event signals different than those reported in allergic rhinitis.

As I mentioned, we've also received poison center data from the toxics exposure surveillance system database for the past five years and confirmed no new adverse event signals in this base and no new medical issues from that in the Claritin database.

Further testing to the safety of Claritin for OTC CIU. The Schering database includes significant OTC experience from 33 countries where Claritin has been sold OTC and in most the OTC indications include skin allergies, urticaria, hives,

and skin itching.

Looking specifically at two of these countries which have had the most significant OTC exposure and where the labeled indications include hives and allergic skin conditions, the marketing experience in Canada and the U.K. include over 38 million patient days of exposure. These data demonstrate that the safety profile of Claritin OTC is very similar to the extensive world-wide prescription experience and the CIU experience is similar to the allergic rhinitis experience.

To summarize, the extensive world-wide experience with Claritin supports the appropriateness of this drug for OTC use based on both Rx experience for CIU as well as OTC experience for hives.

In examining the benefits of OTC availability of Claritin with CIU labeling, our research showed that the current practices and standards of care by physicians and patients treats CIU as a self-managed condition following initial physician diagnosis. Through multiple refills of prescription drugs, primarily non-sedating

antihistamines, the combination of non-sedating antihistamines and current OTC medications and the lack of continual physician care indicate that with the limited physician oversight that this is a self-managed condition largely.

Secondly, consumers already self-treat with sedating OTC antihistamines despite the lack of label indications for this use. A safe OTC product which provides appropriate directions, warnings, and precautions as well as education for proper use including when to see a physician, will provide a significant benefit.

CIU patients who physicians and patients alike acknowledge can accurately self-recognize recurrent outbreaks should have ready access to first line non-sedating therapy as needed to relieve their symptoms.

Making a first line, non-sedating antihistamine available OTC with proper labeling and patient education as proposed by Schering will be a benefit to public health. Based on these facts and the current significant use of prescription Claritin

for CIU in the U.S., we believe it would be inappropriate to switch Claritin OTC without labeling for this indication. Otherwise, we will continue to facilitate off label use of OTC antihistamines for urticaria.

In sum, we conclude the risk of OTC indication of CIU for Claritin is low and the benefit to public health is significant. In addition to easily understandable OTC labeling, Schering is committed to consumer education programs to better educate CIU sufferers as to proper care for their disease. While the specifics of the program have not been finalized, we expect to include education on allergic rhinitis as well as CIU and to focus on educating about the conditions, helping the consumer understand if Claritin is the appropriate drug for their situation, advising when to consult their physician or seek medical care and when emergency care is appropriate.

There are a number of platforms that we expect to utilize in this program including Internet-based information, toll free telephone, print and

continuing education for health professionals.

In the briefing book that FDA provided to you, FDA has asked the committee to address a number of questions which we believe are appropriate for the decision to switch Claritin for CIU in an OTC setting. We believe that the answers to all of these questions are supported by data presented this morning and are supportive of OTC approval.

First, the data support the accurate self-selection of consumers following a physician's diagnosis. Overwhelmingly, physicians and CIU sufferers indicate that they can comfortably and accurately self-recognize recurrent episodes. Although FDA raised some issues about some aspects of certain of these studies, it is clear that the results are remarkably consistent across all studies in confirming self-management.

The self-recognition study demonstrates 94 percent accuracy in patient self-recognition of episodes following initial physician diagnosis. As pointed out in Schering's briefing book to the committee, there is adequate precedent for the

proposed approach of requiring an initial physician diagnosis for OTC products including the vaginal antifungals which were introduced OTC in 1991 and the most recent example of OTC migraine products.

You will note that the label of the OTC migraine products has a statement, "Ask a doctor before use if you've never had migraines diagnosed by a health professional." We would propose similar wording for an OTC hives indication.

In light of the common use of OTC antihistamines for hives, OTC labeling for CIU will unquestionably be a positive step forward. We recognize that there may be likely use by some of Claritin OTC by acute hive sufferers. However, we know that this is occurring today with sedating antihistamines OTC without benefit of any labeling to instruct the consumer how to properly use the product or when to see a physician.

We also acknowledge that there's a benefit in use of Claritin for symptomatic relief of acute hives and there's likely little increased risk in doing so. However, we believe it is more appropriate

and prudent as a first step to label the product solely for chronic hives of an unknown source and encourage proper diagnosis for all other hives sufferers. We are, however, open to continued discussions with FDA to explore broadening the indication for general gives with appropriate labeling and label comprehension testing.

We believe that the OTC labeling for CIU can be improved and we are working to do just that. However, the results to date clearly indicate that this can be achieved. We will work with the agency to refine the labeling to make it even better than the labeling that we tested. We are strongly encouraged by the results of the first study and are confident that we can accomplish this.

We are also committed to an unprecedented consumer and health education professional program to better educate both the treatment of allergic rhinitis and CIU.

You will be asked in you deliberations to consider a number of questions by FDA. I'd like to share Schering's point of view on those questions.

First question, is urticaria a disease process appropriate for an OTC indication? Based on a careful review of the disease, standards of care and consumer and physician practices and self-management, we believe the answer is yes.

The second question. If yes, should the indication be for chronic idiopathic urticaria or hives or should it be broader such that it includes acute urticaria and hives? Our data, as we presented this morning, support the indication of chronic idiopathic urticaria following an initial physician diagnosis.

The next question is, if your answer to question one is yes, are there sufficient data to support an OTC switch of Loratadine for CIU or a more general urticaria claim? We believe that the data we presented this morning are sufficient to justify a switch of Loratadine for CIU. The safety and efficacy of Loratadine in this indication along with the OTC international experience are consistent with OTC standards. While we will refine the labeling for this indication, we believe no additional studies beyond

that are necessary.

The second part of the question. If not, what other types of data are needed such as clinical trials, safety, efficacy, label comprehension or actual use. As I mentioned, for CIU with an initial physician diagnosis, we believe no additional studies are necessary. But if the committee and FDA determine that a broader hives indication is warranted, we do not believe additional clinical trials are warranted or necessary. It is recognized that acute hives and CIU have common mechanisms. The standard of care is the same for both. Efficacy is acknowledged as the first line therapy for both of these is non-sedating antihistamines.

In the case of Loratadine, the safety has clearly been established through international OTC experience in treating hives including acute hives. Further, we do not believe the actual use studies in this condition are either practical to conduct or of value. We believe that any questions could be answered through additional label comprehension testing.

The final question reads, if your answer to question two is yes, what are your recommendations for appropriate labeling of Loratadine with regard to indications, warnings and directions? We have provided draft labeling in our NDA submission which we believe provides the appropriate indications, warnings and directions. Specifically, the use statement, relieves and reduces itching and rash due to recurring or chronic hives of an unknown source. Use only after being told by a doctor that you have recurring or chronic hives of an unknown source.

In conclusion, based on the extremely favorable risk benefit analysis and in light of the current consumer/physician practices, we recommend that Claritin be approved as an appropriate safe and effective therapy for treating symptoms of previously diagnosed chronic idiopathic urticaria in an OTC setting following an initial physician diagnosis. Our expert panel review concurred with this recommendation.

Although we believe this approach for OTC labeling is conservative and prudent, we remain open

to exploring a broader hives indication through additional label development validated through label comprehensive studies if the advisory committee and FDA recommend this approach.

Thank you very much for your attention this morning. My colleagues and I will be pleased to respond to any questions that you may have at this time. Thank you, Doctor Cantilena.

DR. CANTILENA: Okay. Thank you, Doctor Clayton and other members of you team. I think we have plenty of time now for questions for the sponsor. I guess you can identify who specifically of the sponsor team that you're asking or just ask in general and it'll be handled by Doctor Clayton. Questions from the committee members. Doctor D'Agostino.

DR. D'AGOSTINO: My comments are dealing with the particular consumer studies and the label comprehension. I'm not sure from the way the presentation is made that these questions I think are profound or needed because we keep hearing that even if the consumer doesn't have the CIU but has some other type of hives and what have you, you still

should give antihistamines and so I think a question that ultimately we have to or will get to is how do you handle this whole bag of conditions that antihistamines work for.

I'd like to have on the record that I don't think that the consumer study and the label comprehension study are necessarily powerful studies for the comprehension that is being suggested. I think a 70 percent comprehension leaves a lot to be desired and I think that we may say it doesn't make a difference whether the consumer understands a particular condition, he or she still should be taking the drug, but 70 percent with a margin of error of 10 percent is not very large so I'd like to ask the company, the sponsor, to comment on why you're suggesting 70 percent is indicating good comprehension.

DR. CLAYTON: I think our intention there was to indicate that we are encouraged that we can get there to the level we would like to achieve. As Steve Neuman mentioned, the principal display panel was broader probably in terms of stating what the product

use was. The drugs facts box that I showed you in the next to last slide was a lot more specific. We believe that the labeling can be improved and our standard is higher than the 70 percent, too. We would expect to achieve that.

DR. D'AGOSTINO: I have just two other questions and I'll move fast because I know that people have a lot of questions. With the random sample and the consumer study, you took a random sample and they were supposedly a validation procedure where you rescreened the individual. Could you tell us how many individuals were selected for the random sample and how many out of those didn't actually have the CIU condition on the rescreening in terms of the validation. I'm not sure I heard that number.

DR. CLAYTON: Steve, would you please come forward and respond. He's checking his notes.

DR. D'AGOSTINO: And my last question, while you're fishing that out, it again may sound naive but if we're saying that these potpourri of conditions can be handled by antihistamines and you're focusing on the CIU, I know it's in the Rx, but why

aren't we hearing a presentation for the broader condition? You're telling us that people are using it for broader conditions and it appears to me once it goes OTC, if it goes OTC with this label, physicians are going to be telling patients to use it for the broader array of conditions. Why aren't we hearing the sponsor saying something in defense of that as opposed to that's what you do and it's off label? Those are my three questions.

DR. CLAYTON: I can respond to that one while Steve is preparing. The prescription indication is chronic idiopathic urticaria and that's what led us to do the research that we conducted about the appropriateness for OTC use. So that is the basis for our interest in CIU and that is the research that we've conducted. So that is the area where we are most comfortable that the data support OTC use and indication.

I mentioned that there is wide-spread international experience OTC with a broader indication and we are open to continuing to pursue that, discuss that with FDA. It's certainly not a closed door but

our research today most strongly supports CIU following an initial physician diagnosis.

DR. D'AGOSTINO: Thank you.

DR. CLAYTON: Steve I think has the response.

MR. NEUMAN: There were 81 individuals who did not suffer CIU at the re-qualification phase.

DR. D'AGOSTINO: So about 25 percent of the sample --

MR. NEUMAN: The outgo was 834. One hundred ninety two did not log in. One individual was not 18. Eighty one worked in a sensitive occupation such as marketing research, advertising and so forth. Then 81 did not suffer CIU at the re-qualification phase and another logged on after the survey period closed.

DR. D'AGOSTINO: So 10 - 20 percent said CIU.

MR. NEUMAN: About 20 percent.

DR. D'AGOSTINO: Thank you.

DR. CANTILENA: Okay, Doctor Krenzelok.

DR. KRENZELOK: Thank you. This question

is for Doctor Monroe. The literature that we received from the sponsor indicated that urticaria is often an expression of a number of very serious diseases, urticarial vasculitis, thyroid conditions, cancer and so on. I just wondered if chronic use of something like Loratadine would mask the diagnosis of some of these more serious diseases and delay their treatment.

DR. MONROE: Approximately 90 to 95 percent of the cases of chronic urticaria are idiopathic so the percentage that have an underlying disease would be very small to begin with and the more serious ones that would concern me the most that are systemic in nature such as a connective tissue disease or vasculitis, I would say the incidents might be less than one to two percent of the total. Those patients also should have other signs and symptoms. So for example, on the connective tissue diseases, one would expect arthralges, fever, fatigue, other systemic signs. There are in urticarial vasculitis signals such as the lesions persist longer. There are some signs and symptoms that I think would lead those patients to go consult the physician.

So I think the concern potentially in that small subset is a delay in getting to the physician but I think the persistence of their condition since the underlying cause for the urticaria is there and the possible accompaniment of these other signs and symptoms would eventually leave them with a mild delay to the physician anyway.

DR. CANTILENA: Okay. We have Doctor Szefler and then Doctor Sachs.

DR. SZEFLER: Two questions for Doctor Monroe. In treating the disease and also looking at all the review articles that were provided, it was a very nice package. I didn't get any indication that Loratadine had a specific effect on chronic urticaria. In other words, if a physician was choosing an antihistamine, would they choose Loratadine over the other three drugs? Is there any reason to believe that Loratadine confirms unique features in terms of drug selection? And then also the situation a physician runs into is the necessity of using higher doses to treat the disease. How will the package insert or how do you anticipate physicians will handle

the use of higher doses potentially for prolonged periods of time and is there any unique feature that the physician should be concerned about in the OTC application?

DR. MONROE: Your first question I think centered on did Loratadine have any unique properties versus you said the other three. You mean the other approved for prescription?

DR. SZEFLER: Yes.

DR. MONROE: Okay. I believe that the currently available second generation H1 antihistamines are all relatively equally efficacious and the difference lies that at least one of them is sedating. So I think that Loratadine doesn't offer any unique property. It offers an equally excellent property.

The second question I think centered around a concern over exceeding the currently recommended dose and my answer to that would be there are anecdotal stories from patients and certainly use by some physicians exceeding the recommended doses of all the second generation antihistamines. I am not

aware of any scientific study to show that doses beyond the approved doses are more effective and, as a matter of fact, in the initial Loratadine approval or clinical studies, doses ranged from 10 to 40 in chronic urticaria and there was no added efficacy beyond the 10. So it does occur in practice. I can't support it from any scientific study and I think that I'm not a labeling expert but one would just deal with it in the labeling like they did for the prescription.

DR. SZEFLER: So your suggestion might be in labeling that a preferred route of additional treatment might be to use an additional drug rather than increasing dose.

DR. MONROE: I'm not a labeling expert. My recommendation, if they came to my office, would be that they should see the physician at that point. If the standard of care wasn't sufficient, I think that's where the physician should be involved.

DR. CANTILENA: Doctor Sachs and then Doctor Davidoff.

DR. SACHS: Hi. You guys look like the label indication is going to go down to age six. From

the studies presented today, it sounded like most of the studies were people over 18. The study packet we received, I think the lower age limit was 12. So I was just curious about pediatric data. Unfortunately, in my experience, one of the differential diagnoses of chronic urticaria in children is leukemia and granted, the symptoms would persist and cause a parent to seek help for their child, but I was just curious what the studies in kids were.

DR. CLAYTON: I'd like to call on my colleague, Doctor Patricia Rohane, a physician in Schering-Plough, to respond to that question.

DR. ROHANE: Yes. Thank you. With respect to the safety data that we have in pediatric subjects, we've conducted three placebo-controlled studies. In these studies there have been enrolled around 350 children. The ages have ranged from six months up to 12 years and, as I said, the safety events in these children have been compared to placebo and the adverse event profile has not been different. In other words, the events we saw in the children on the active treatment were the same as; those seen in

the placebo groups.

DR. CLAYTON: I would also like to mention the syrup product is labeled as approved down to age two and our experience in Canada and the U.K. with OTC products, those products are labeled down to age two including skin allergies as well as allergic rhinitis. So our database of experience includes down to that age group.

DR. CANTILENA: Okay, Doctor Davidoff.

DR. DAVIDOFF: Yes. I think the studies on the population with pretty well defined CIU are at least moderately reassuring but I think the larger or perhaps the more important question lies with the understanding and behavior of everybody else because 97 percent of the population or more doesn't have CIU and yet this medication would be available to them as are now of course the more sedating antihistamines. Seems to me that your data rather elegantly demonstrate that before the diagnosis is made the great majority or at least the majority of the population either don't read the labels or they don't understand them or don't believe them because they

don't follow them. They use sedating antihistamines now for any itchy condition that they don't understand. So I was rather struck by the minimal amount of data on the general population. Perhaps you could give us some thoughts on whether more data really are needed before we go ahead.

DR. CLAYTON: Steve, do you want to comment on the label comprehensive studies that relates to the general population?

MR. NEUMAN: Yes. The general population in terms of the label comprehension. Label comprehension was sound on all of the general warnings. It was really in the self-selection area that there was probably one of the largest issues with 30 percent inappropriately selecting the products and, as we indicated earlier, we think that that's not as high as it should be and we would definitely recommend continued work on the label to improve that level.

DR. CLAYTON: As you pointed out certainly, the current practice now is that there is significant off-label use and, as we improve the label, we think we will set a higher standard of

education for the general population with labeling that specifically advises on the appropriate use and the appropriate precautions and warning statements.

DR. DAVIDOFF: Thank you. Could I ask a brief related follow-up question and that is I was curious about the low literacy population because my understanding is it's somewhere in the range of 15 to 25 percent of the population is functionally illiterate and particularly when it comes to medical information. I was curious how you were able to get the low literate population to read the labels.

DR. CLAYTON: Steve.

MR. NEUMAN: The low literate population was recruited from special sites that have been targeted as places where these individuals can be found at higher proportions in the population. The label was presented to them just as they were in a store potentially looking at it for purchase and the numbers actually were fairly encouraging among that cohort. They were lower than the general population by a few points but across the board there was relatively good understanding of most of the general

warnings.

DR. CANTILENA: Okay. Doctor Dykewicz, please.

DR. DYKEWICZ: I have several questions and comments. The first would be about the consumer study. As Doctor Monroe has pointed out, one of the concerns historically that would identify potentially a more serious underlying problem might be the symptom of joint complaint. In the consumer study, was there any question that addressed that particular issue?

DR. CLAYTON: Steve.

As he's coming to the microphone, I would point out that the draft labeling did include a precautionary statement on joint pain to not use the product but seek medical care as far. As the testing is concerned, Steve can respond to that.

DR. DYKEWICZ: And as he's approaching the microphone, besides the joint ache question, it would be how representative the study group was in terms of education versus the general population.

DR. CLAYTON: Okay.

MR. NEUMAN: I can address both of those

questions. There was a question that was asked regarding symptoms that have been experienced and joint pain was experienced by 14 percent of the sample CIU population. There's not a lot of specificity beyond that as to what type of joint pain or the characteristics of that joint pain but 14 percent did experience that.

With regard to the Internet and less educated populations, the Internet does under-represent less educated populations to some degree but what we did was we did an analysis where we looked at those who were less educated among our consumer population which was high school and less and compared that to those with a bachelor's degree and higher. What we saw across most of the key questions was that there was really no difference in response.

DR. DYKEWICZ: Okay. I guess it still raises the issue in my mind though relative to the joint complaints that that was not something that was focused on relative to whether this would be a cause for seeking attention of a medical provider.

Another question about the label

comprehension study. I guess I'm a bit perplexed. On one hand, we see that 30 percent of the respondents gave incorrect answers for self-selection and sponsor I think appropriately is saying that some improvement of the draft labeling would be required. But it also is the position of the sponsor that no additional label comprehension studies would be required in that vein?

DR. CLAYTON: No. If that has been the message we've delivered, that is not the correct message. We believe the labeling can be improved and we would test the labeling that we believe would be more appropriate for the market place.

DR. DYKEWICZ: Okay. Thank you. And one last comment. The statement which I think is generally correct that chronic urticaria is not associated nor is it a risk factor for anaphylaxis is mostly valid but I would point out I was involved with Northwestern University's series of patients with idiopathic anaphylaxis who did have life-threatening manifestations at anaphylaxis and looking back historically, about 50 percent of the patients in that

series did have a pre-existing history of idiopathic urticaria and angioedema. So while I agree that in general for the population the presence of urticaria probably does not identify a significant major risk for development of more severe manifestations including anaphylaxis, there may be certain notable exceptions to that.

DR. CANTILENA: Other questions from the committee? Doctor Rosenberg.

DR. ROSENBERG: I have questions, not about the presentation we heard but about the written submission from Schering and specifically under Tab 7, confidential physician habits and practices study and specifically on page 24 which is your slide for question 15b. I'd like to ask, I suppose, Doctor Monroe, to comment on it. What this addresses is, of course, if it's not OTC, it's in the hands of the profession and I think I don't know if this is the only time, maybe this afternoon, but we ought to look at what the profession does.

A couple of points I wanted to make. One, under primary care practitioners, it's a mix of

family doctors and internists and our experience in a medium size city and a disease that's not so serious and where it's hard to get an appointment with a doctor, particularly a specialist, that much of the urticaria patient population we see have come from a walk-in clinic, a minor, open late hours type store front clinics which some of them are under hospital ownership but which are a feature of medical care in our community and I think were they to have been included, 100 percent of those people got prednisone. They all get prednisone.

The line I want to talk about is where systemic steroids are, as I understand the question, the medication most often prescribed by the treating physician and it shows that these primary care internists, pediatricians -- I mean pediatricians, 28 percent choose systemic steroids first . The allergists in my opinion do somewhat better at 22 percent.The primary care people, as I say, 41 percent and if you include the walk-in clinics and emergency rooms, it's 100 percent, and the dermatologists, only 12 percent which I think is certainly the best of

those and I want to ask Doctor Monroe, A) which he thinks would be more likely to mask some serious underlying disease. The use of Loratadine or prednisone. And B) would he comment on the appropriateness of prednisone under most circumstances as a first treatment and would he be more comfortable prescribing prednisone if the patient had first treated themselves with, when available, OTC antihistamine and came in and said I can't sleep despite I take all that stuff. Can you help me?

DR. MONROE: Okay. I am not familiar with the section that you're referring to but I think I understand your question and I appreciate the compliment that the dermatologist had the best percentage of not using systemic steroids.

I think there is a concern that primary care physicians as well as ER or urgent care physicians tend to turn more, particularly in acute urticaria, to the use of systemic steroids. In a treatment algorithm of what I believe is appropriate therapy, in acute urticaria, I believe that the first choice is the use of the H1 antihistamines and the

second choice for a severe case would be the use of systemic steroids because you assume you've got a fairly self-limited condition.

I'm very reluctant to suggest that systemic steroids should play a regular part in the treatment of chronic urticaria where I think you have more risk of introducing more serious problems from the treatment than you do from the condition that you're treating.

I think systemic steroids have a very possible likelihood of masking the underlying problem but if the underlying problem is there, I'm assuming we're talking about a short course of let's say oral steroids. The steroids will wear off and I think you're again back to the baseline that if you have a persistence of the signs or symptoms of the urticaria or of some other systemic symptoms, the patient should see their physician. I think if a physician gave systemic steroids in an IM form, something which I don't recommend, you might mask it for a longer period but I think you're again back to the situation that if there's an underlying problem, whether it's the

antihistamine or the steroid, masking will be very temporary and you're back to hopefully seeing a physician for further evaluation. I hope that answered your question.

DR. CLAYTON: Perhaps we're on target with our commitment to an educational campaign that includes health professionals if we go forward here.

Doctor Joad.

DR. JOAD: Yes, I have a question follow-up to Doctor Sachs' question which is it's not clear to me that we have a study that shows how well people recognize hives versus non-hives. For instance, how able are people to recognize hives as compared to purpura or something that would be not even hives. So the differential that we've been talking about is a high differential but what about all other ashes that might also be really important to look into? Are there studies like that or is your company considering doing or should your company do it?

DR. CLAYTON: I'm not aware -- I don't know whether Doctor Monroe is aware -- of studies that are as you describe. Certainly our experience in the

self-recognition study showed a very good correlation of patient and physician recognition or diagnosis, if you will, in this case, of chronic idiopathic urticaria.

Doctor Monroe.

DR. JOAD: But those patients had that condition.

DR. CLAYTON: That is correct.

DR. JOAD: That is not the general population.

DR. CLAYTON: That is correct.

DR. MONROE: And I think that's one of the reasons why there's a higher comfort level for the chronic idiopathic urticaria indication because those people by definition have usually consulted a physician, understand what they have whereas what you're saying, there could easily be a broader array of confusing dermatologic problems that the layperson might not be able to accurately diagnose. I think that can be addressed, but the comfort level in CIU is that there is a significantly high recognition level. In the broader population, I think that presents more

of an issue. I think the point I tried to stress was the situations where that confusion would occur would most likely not result in a serious problem but if somebody had, for example, purpura that you alluded to, I consider that a much more significant issue that would require seeing a physician. Whether the patient or consumer would be comfortable in making that distinction is very debatable.

DR. CLAYTON: On additional point is as we are evolving our labeling, the labeling that was tested, we've tried to put precautionary statements that would steer a consumer to a physician if in fact they don't experience relief within a matter of a few days and, again, as we move forward in refining that labeling, that will be a consideration that we would certainly take.

DR. CANTILENA: Doctor Johnson.

DR. JOHNSON: I'm wondering if Doctor Monroe can educate me a little bit about angioedema since this might be one of the conditions confused. I guess my confusion is based in part on my general impression of angioedema and there's also a drug under

review by cardio-renal that has angioedema as a side effect. There's apparently very, very significant concern, certainly in the community that would use it, if that drug is approved. My understanding is that in most cases the angioedema was not serious and so I guess the presentation here presented angioedema as something that is not serious and yet in other settings it seems to be something that's taken very seriously. So I'm wondering if you can sort of clarify.

DR. MONROE: The vast majority of people who have angioedema who have it in soft tissue areas, let's take the non-laryngio, non-oral, which is the vast majority, I view that as a more visually upsetting but similar process to urticaria. I think the issue with maybe the drug you're alluding to and the medical concern would be angioedema affecting the oral cavity, the larynx so that you might then develop the respiratory compromise and that kind of concern and that I do consider a serious issue. It's a much, much less frequent issue than the general angioedema because I think the studies would indicate that about

40 percent of the patients who have urticaria have concomitant angioedema and maybe another 20 percent have urticaria alone and another 20 percent have angioedema alone.

So angioedema is not that uncommon of a problem. It's that rare situation when you have, for example, the lorengio edema that causes us concern and that causes me concern as well and that's why I think there was an attempt to state that any symptoms of respiratory distress, wheezing, difficulty of that nature, would have to be appropriately labeled and patients educated as to the seriousness of that potential.

So I think what the concern is on that very small percentage who have angioedema in that anatomical region.

DR. JOHNSON: So those people, the 40 or 60 percent that have angioedema but not lorengio, they're not at risk for lorengio angioedema?

DR. MONROE: The vast majority of people who have angioedema have it in other soft tissue areas that would not be of medical significance and, again,

we're not talking about the exceptions like the hereditary angioedema in that either. So the vast majority, I believe it's just concomitant as part of their general urticaria and the treatment would be the same as the general urticaria.

DR. CLAYTON: I'd just like to underscore Doctor Monroe's comment about labeling because we do have in our graph labeling any respiratory difficulties as seek emergency medical care. We're certainly sensitive to that possibility.

DR. CANTILENA: Doctor Uden, then Doctor Szefler.

DR. UDEN: I'd like to know the incidents of chronic idiopathic urticaria across races and I didn't see any information presented in your documentation about the demographics, racial demographics of your self-recognition study and your label comprehension study. Do you have that information?

DR. CLAYTON: Yes. Steve.

MR. NEUMAN: As for race and CIU, in the literature that's been reviewed, there is no

proclivity for any one race to have or any sort of racial skew toward any group to have CIU.

With regard to our studies, the profile of the consumer study did somewhat under-represent non-whites, particularly blacks, but there was a bit of a confusion here in that some of those subjects indicated that they would not respond to the question. So it's a little difficult to determine in that study exactly what the African-American population was.

And the label comprehension study, I'll have to look that one up.

DR. UDEN: While you're looking that up, could you clarify what you just said about the African-American population. I didn't understand that.

MR. NEUMAN: I'm sorry. About the effort in the Internet study or in --

DR. UDEN: You just made a comment about the African American population, that they didn't respond and what study was that?

DR. CLAYTON: Oh, that was the consumer study. In the consumer study, there was a relatively

low proportion of blacks who were indicated in the demographic profile. However, it was a little confusing because it was like in the four percent range. But there was about six percent, as I recall, who just did not respond to the question at all. So it's difficult to determine what the racial profile of those individuals might have been. So it's hard to say how under-represented it is. Is that clear?

DR. UDEN: I'm a little closer but not there yet.

MR. NEUMAN: It's not definitive. We have four percent that actually signified African-American. There were six percent that didn't declare. So we can confirm that four percent did say they're African-American. The other six percent we don't know how it's made up according to race.

In the label comprehension study, the white population was 84 percent, black African-American two percent.

DR. CANTILENA: Okay. Doctor Szefler and then Doctor Joad.

DR. SZEFLER: I'll speak to Doctor

Clayton. Much of the discussion this morning and much of the literature that came to us was centered around the product information or the labeling, but another big area of contact with patients is direct patient advertising through television, through magazines. When I looked at your list of consumer health profession education programs, I didn't see this included. I wondered what your thoughts were. Was it intentional not to put these sources and what's your plans for the future in terms of advertising since this is such a confusing issue and since the chronic urticaria is a minor population in terms of the urticaria presentation. How do you plan to interact with the public in terms of these media?

DR. CLAYTON: Obviously advertising is not set so I really can't comment on the composition. Hopefully our advertising would be educational also to help patients clearly understand the appropriate product or if this is an appropriate product for their condition. We think that there's very limited, certainly in the media, the non-print media, it's very limited time element to provide that kind of

education. Our better hope would be through print. In the draft, the outline of our educational program that included a number of different vehicles including print along with Internet and other forms or other platforms of communication.

But the answer is we have not established that but we certainly understand the importance and value of educating the consumer about this drug and its uses, not just urticaria but also allergic rhinitis.

DR. CANTILENA: Doctor Joad.

DR. JOAD: For Doctor Monroe. What percent of the patients with chronic idiopathic urticaria are children? I think some of the articles said it was a middle age disease primarily. I'm just trying to get a sense.

DR. MONROE: I don't know the answer. The highest incidents of chronic idiopathic urticaria is in middle aged women and definitely the urticaria we see in the pediatric age group is more commonly the acute, but I don't know the exact number for chronic idiopathic urticaria. It would be small.

DR. CANTILENA: Doctor Davidoff.

DR. DAVIDOFF: Also a question for Doctor Monroe. It gets back to the issue of potential difficulties or harms that might come from delay in diagnosis because you pointed out that if there is a negative effect of release as over-the-counter drug, it's not likely to be negative in the sense of direct harm from the drug but rather from delay or some non-optimal care pathway.

On the other hand, it's also pointed out that there's been no reporting of signals of events that might be red flags that there might be some such problems occurring. On the other hand, it's also known that the under-reporting problem is enormous, even for direct harms from drugs. So what I'd like to ask you to do is to give us your best estimate. What would be found if reporting of delays and the potential harms that came from them were perfect? What would you speculate would be the kinds of harms and less than optimal care that might result from such delays, both in the CIU population and perhaps in the more general population?

DR. MONROE: In the CIU population, I'm making the assumption that they have seen a physician to get that diagnosis, so I don't see any added harm. Obviously there are some people that we would diagnose as CIU that as time evolves maybe we come up with an answer for an underlying reason. So I don't think that changes the CIU scenario.

In the general population, I tried to give a quick overview. I think there are situations with some very common conditions. The acute urticaria that may be confused. I think that in that situation the treatment is what the physician would have prescribed anyway except that we're introducing a safer treatment than the OTC. I think in the common dermatologic conditions that are not urticaria, the dermatoses, I think the patient is not necessarily capable of distinguishing an itchy rash. For physicians in the room, we often get calls, I have a rash, what can you prescribe? And I say there are a million different rashes. So I think that's a problem. Fortunately, I believe most of those rashes don't present a serious consequence if there's a delay. There may be a

quality of life consequence that they have a few extra days or weeks of less than the appropriate therapy.

I think there would be the rare rash, if there's purpura or some severe vesicular bullous disease that the patient would not be able to identify, but I think those would be extremely infrequent. So I think in general my message would be that there would be delays of inappropriate diagnosis and treatment but I don't think they would be causing harm.

DR. CANTILENA: Any other questions? Doctor Wood.

DR. WOOD: It seems to me that we heard a fair amount of data that patients with CIU can diagnose it probably and treat the condition on their own. The issue though that's still unclear to me at least whether patients who don't have CIU and might be using antihistamines even now incorrectly and I'm surprised there's no data to really address that because you've really sort of addressed, kind of answered the question before you've done the study almost the way it's designed right now, it seems to

me. I was pondering here about how one would do that study.

I guess one way to address that would be to look at patients who are using currently over-the-counter antihistamines and see what the conditions they're treating are with them. I'm not sure what conclusion you'd necessarily draw from that but that would certainly be educational in terms of trying to more appropriately steer patients to the right therapy.

DR. CLAYTON: The only comment I could offer is to your point. I think there is widespread use of over-the-counter antihistamines for those conditions now and, as we've learned in our research, particularly with acute urticaria, most patients don't seek physician care anyway. So it's not a good answer. I don't think that the data exists. Just observations.

DR. CANTILENA: Okay. Thank you. Any other questions from the committee for the sponsor? Doctor D'Agostino.

DR. D'AGOSTINO: The consumer study and

the physician was done by the Internet. Is this sort of a wave to do them by Internet? I mean you leave out a whole class of individuals who can't participate because they're still illiterate computer-wise.

MR. NEUMAN: Yes, it is actually a wave and, in fact, most of the major purveyors of research services have instituted Internet divisions. About 60 percent of the population is on the Internet now and I think that there is an opportunity to see that grow over the next several years.

DR. D'AGOSTINO: We all have personal experiences. I have a few experiences where the Internet connection collapsed so I'm not so sure that it's a wave of the future that is completely solid. Aren't you concerned that you're leaving out whole segments of the population, there's still a 40 percent, who take drugs?

MR. NEUMAN: Well, actually, there are -- as you well may know -- there are issues with nearly every research method. Telephone studies have their issues of non-response and mall intercepts have issues of socio-economic skews, the Internet has some issues

as well. So it's, I guess, a little bit of pick your poison.

DR. D'AGOSTINO: The label comprehension was an all comer study. Could you just remind me how you recruited that sample.

MR. NEUMAN: Yes. It was recruited through malls.

DR. D'AGOSTINO: Through malls. Thank you.

DR. CLAYTON: And to your point, Doctor D'Agostino, obviously the most critical study, the label comprehension study, is the old fashioned way. Individual contact, not through Internet.

DR. D'AGOSTINO: Not necessarily the best but at least --

DR. CLAYTON: Accepted.

DR. D'AGOSTINO: -- you hope to see everybody.

MR. NEUMAN: One other point though. The CIU population was recruited through advertising in the papers.

DR. CANTILENA: Okay. And our final

question from Doctor Gilliam.

DR. GILLIAM: Getting back to Doctor Uden's question about other populations that were surveyed for the label comprehension. How about Hispanic populations? Spanish labeling. Anything done in that area?

DR. CLAYTON: No. Nothing has been done to this point in that area.

DR. CANTILENA: Okay. I wish to thank the sponsor and the committee for their questions. We will now take a 30 minute break and report back at 10:30 for the FDA presentation.

(Off the record at 9:57 for a 33 minute break.)

DR. CANTILENA: The next section of the agenda deals with the presentation by the Food and Drug Administration. The lead-off speaker for the FDA will be Doctor Jonathan Wilkin and then he will introduce the subsequent FDA speakers. Doctor Wilkin.

DR. WILKIN: Thank you, Doctor Cantilena.

Members of the Advisory Committee, I will give some brief comments, much briefer than what I had

originally planned after the very nice presentation of Doctor Monroe and his colleagues.

Doctor Monroe has seen this slide before. I've nominally plagiarized it for today but actually he published this in 1977 with Earl Jones, and I've used it since 1978 to the present at least 15 times to give the conceptual architecture of urticaria to sophomore medical students and, of course, the residents in our training program. Basically, the very nice piece is we've got the immunologic factors that act on the mast cell or basophil and the non-immunologic factors that connect on the mast cell or basophil. So a wide variety of etiologies, different causes that can act on the mast cell. And then there are some modulating factors, those things which can either act on the mast cell itself or can act on the small blood vessels to increase the diameter and potentiate the effect of the released mediators.

But at any rate, the mast cell has only one basic trick. It releases this vesicle exocytotically, release mediators, histamine is the principal one, and it acts on the small blood vessels

and the upper skin to produce urticaria.

This is another slide plagiarized from Doctor Monroe. What I did in the medical school classes was I started out with just the membrane receptors and then I added the intracellular cyclic nucleotide story and I kept adding different intracellular processes until finally at the end the microtubials and the microfilaments steered these vesicles containing hepron and the histamine and all of the other vaso goodies to the surface and then the exocytotic release into the extracellular area.

Where this happens in the skin -- this is Frank Netter's nice drawing of the skin and up here at the top you can see arranged in layers like baklava the epidermis and then from here down to here is the dermis. Here's the subcutaneous fat, the butter, and it's in this very upper layer here where there's a superficial vascular plexus and that's where the mast cells release the histamine that leads to the urticaria.

We'll see the two plexus because there's another plexus that's down deep in the next slide so

that for the typical urticarial kind of lesion, it's going to be leakage in the superficial vascular plexus. That's where the histamine is released and acts on these vessels. For angioedema it's going to be the vasculature that is in the superficial subcutaneous tissue and the very lower dermis at that interface. But they are very similar processes. One of the key differences is that the nerve endings, the C fibers, the itch fibers, are predominantly located up in these finger-like extensions up into the epidermis, the dermal papillae. So hives itch a lot more than the angioedema kind of lesions that will form deeper.

This is looking at one of those finger-like projections up into the epidermis. Here's the arteriolar part of the superficial vascular plexus and it goes up through the arteriolar side of this capillary loop and finally back down on the venular side of the capillary loops to the post-capillary venial and this is the site right here that really is where histamine acts and the endothelial cells pull apart and the fluid leaks out. That is where the

urticarial lesion really occurs. And so it's a very superficial kind of leakage of fluid, so superficial that it puffs up and you can actually run your finger over lesions of urticaria and at the edge you can find that it'll actually lift up to this flat kind of surface.

Over a few hours time, the edges of the typical urticarial lesion will migrate and so they're not fixed kind of lesions.

These are the smaller, average size urticarial lesions. Sometimes they can be really large. They're not necessarily angioedema. Angioedema, when you put your hand on the skin, it feels like wood. I mean it's really got a thick indurated kind of quality to it.

So the key piece is that there are literally hundreds of causes of urticaria and they either act directly or through the immune system to cause mast cell mediator release which then these mediators are released in the area of the small blood vessels and principally histamine leads to the itching and the edema, the fluid leakage.

But there's also another way of looking at urticaria, the heuristic or clinical ways of looking at it. This is very similar to the industry's presentation because I think most physicians use the same system. Acute urticaria is less than six weeks in duration, has an incredibly good prognosis. Most of it is actually gone by six weeks. It's only down in the five percent range that extends beyond. History implicates the cause in approximately half of the patients. If they come to the emergency room or to the dermatology clinic, they're seeking symptomatic care but very often they know what the inciting event was.

I think it would be very difficult to study acute urticaria in clinical trials just because you would almost have to know who's at risk for developing acute urticaria before they actually developed it and since it has such a great prognosis and may only last a week or two, it would be hard to get these people in in time to actually give them medication and monitor them for any length of time to get a signal. So very difficult to study in clinical

trials.

There's a distinction between chronic urticaria and chronic idiopathic urticaria. Chronic urticaria means greater than six weeks. A work-up is indicated because perhaps five to 10 percent of those patients will have a definable cause that can be detected in the office of the allergist or the dermatologist. These would be much easier to study in clinical studies because often they are persistent. So you can give them medication for a period of time and they're not likely to have a spontaneous remission.

The distinction between chronic urticaria and chronic idiopathic urticaria means that someone really looked in a sensible way to see if there is a cause and they couldn't find it and so then you can add the word idiopathic. But it's the subset of chronic urticaria in which a good work-up fails to pinpoint the cause. It's a diagnosis by exclusion and obviously it's not homogeneous. There's still a lot of different types of causes. Some of them are going to be direct mast cell mediators. Some are going to

be through the immune system of causes of chronic idiopathic urticaria.

Again I borrowed this one from Doctor Monroe. This is his schema for treating and managing acute urticaria. For the mild and moderate types, he recommends non-sedating H1 antihistamines. I think generally that's the approach most physicians take. So the kind of medication we're talking about today is actually the first choice for most patients who have acute urticaria.

So observations. Urticaria really is not a single disease. It's a reaction pattern mediated by histamine release in the superficial skin. Acute urticaria and chronic urticaria are not single diseases. They're useful for clinical decision making. Most urticaria will respond to an antihistamine which is found safe and effective in patients in chronic idiopathic urticaria.

There are some caveats when thinking about what an OTC label might look like. I think that some of the things that we've already heard discussed. The OTC consumer could be informed. I think there are

some varieties of urticaria that are more likely to get patients into trouble, not because they might be taking this medication but because they might not be seeking the intervention of a physician early on. In fact, for all of these conditions, I'm not sure but what they might actually get a medication like this as part of the therapy. It's just that they need some additional evaluations.

The first kind of urticaria. I think if the patient believes that it's possibly related to peanut or latex allergy because that can ultimately -- the second time around, there may be anaphylaxis. I think that would be a subset that they ought to go and see a physician early on. Persisting beyond six weeks. Again, that's the group where the work-up is indicated and where perhaps up to 10 percent of patients you can actually find an identifiable cause. Often it's something that they can eliminate so that they will not have the continuing urticaria. Or they may have some underlying disease that's leading to the urticaria and the work-up will detect that.

There is a condition called urticarial

vasculitis. One of the features in urticarial vasculitis is the lesion. Unlike usual urticaria, it doesn't really migrate. The edges stay in the same place. You could take a skin marker or a fountain pen or something and draw a ring around where the urticarial lesion is and it will be there 24 hours later. That's not what urticaria usually does. I don't think that point probably would translate in an OTC labeling but because these generally leave a bruising or pigmentation post-inflammatory pigmentary changes, I think that might be something that would get these patients alerted that they need medical help.

Also, when there's something beyond the urticaria that also involves the skin. Blistering is one or again the bruising part. It could be part of the vasculitis or bullous penfogoid.

Serum sickness. Like reactions can have urticaria as some of the features and the connective tissue diseases. But if we had something on labeling that would say something about fever, joint pain, just feeling unwell, systemic features in general, that if

that accompanies the urticaria, then it's important to seek medical help. Any urticaria that's poorly responsive to oral antihistamines also ought to be checked out by a physician and then that variety of angioedema, not the kind that occurs on the arms and the legs and perhaps the skin over the trunk. But if there's swelling of the lips, tongue or throat, again that can be a very worrisome prognostic feature and they should be also seen by a physician.

And then the urticaria which looks like urticaria but it doesn't itch and those may be the infiltrates into the skin of a leukemic process or there are some varieties of urticaria that don't itch so much, the delayed physical kinds of urticaria, and antihistamines don't work really great and so that really means that if it doesn't itch, patient really should see a physician.

Some of these statements I've taken from the sponsor's briefing package, modified them a little. Urticarial lesions are generally easy to recognize since they typically occur in visible locations and are associated with intense itching.

That's on page seven of sponsor's briefing document. I think that's true. I've seen a lot of patients with urticaria and they generally come in and say I've got hives, doc. What can we do?

I would also agree with a second point that they made and this is found on page 18 in the sponsor's briefing document except I added the word sedating in here because I think that's part of the context in which one must think about this. It is likely that acute hive sufferers are already using sedating OTC antihistamines. And so I think this is an opportunity, if this goes over-the-counter for hives, it's an opportunity to put some things in labeling that will direct patients to physicians for some conditions that might be confused with or associated with hives and actually it could be better than the current situation which is they're just using it but they're not getting that message.

And then I think the core piece in Doctor Monroe's message and I think throughout the literature is that the hive and the associated itching of almost all urticaria is mediated by histamine and so one

would anticipate that for almost all varieties of urticaria, an H1 non-sedating antihistamine is going to provide patient relief. And so I think that it would be possible with proper labeling but I think that's really the key thing is how does one get some of these extra conditions in there and explain them to an OTC consumer. It just may be that the hives could be the preferable OTC indication.

The next speaker is Doctor Chowdhury.

DR. CHOWDHURY: Thank you. Good morning, members of the Advisory Committee. I will be talking about the clinical development program that the various companies have done that has resulted in the indication for H1 antihistamines for chronic idiopathic urticaria. The antihistamines that I'll be covering are the newer ones which includes Loratadine, Desloratadine, Cetirizine and Fexofenadine.

In your briefing package you have Desloratadine medical officer review as an example, an example only, of a recent development program for an antihistamine that has the CIU indication.

I will be talking initially very briefly

about urticaria in general and then in a very global sense about the clinical development program for antihistamines for urticaria. Then I'll be talking about specifically clinical programs for antihistamines elaborating more on Loratadine which is a point of discussion and touching on the other antihistamines. And then I'll have some summary remarks.

As we heard before, urticaria is classified as acute and chronic -- duration, the cut-off being six weeks. One thing to keep in consideration which we also heard before that acute urticaria can occur as an early manifestation of anaphylaxis. Urticaria, in addition, can also be intermittent which is in between acute and chronic. Patients have urticaria lasting for days and weeks with intervals which is pretty long in terms of days, weeks or months.

In addition, there can be urticaria where the causes are known, some of the examples being physical urticarias, cholinergic urticarias and so on. As you heard before, the clinical development program

the companies have focused on CIU because these patients have recurrent hives and are expected to have recurrent hives during the clinical trials, therefore, can be studied.

The patients with clinical hives have repeated dermal mast cell degeneration -- antihistamine and other mediators and these cause the typical wheals or the -- lesions. It can occur anywhere on the skin. There are varieties of sizes and shapes and they're paler in the center with redness in the surrounding area and the individual wheals last for a short duration and there's entrance itching around the wheals and there is often -- redness of the skin. These are the features that are used in evaluating efficacy end points for patient evaluation in the clinical urticaria trials which I'll go into later on.

For the CIU indication, the FDA requires evidence of efficacy from at least two clinical studies including exploration of the proper dose and demonstration of the safety of the proposed dose. The pivotal efficacy studies are randomized, multi-center,

double-blinded, placebo-controlled and often they are active-controlled. Most of the pivotal efficacy studies are four to six weeks in duration. In addition, the safety of the proposed dose must be demonstrated.

In addition to the pivotal efficacy studies, the companies often does what is called a wheal and flare study. These are pharmacodynamic studies where small amount of antihistamine is injected under the skin to cause an artificial urticarial-like lesion and histaminic effect is tested on those lesions. These are peer pharmacodynamic studies and are not taken as reflective of evidence for an antihistamine effect or for an evidence of efficacy for urticaria.

The patients enrolled in the CIU studies are generally adults. In various studies, they have been 12 years or older. In others, 18 years and older. And they're free of clinically significant diseases. Pediatric indications for urticaria are usually given by -- based on pharmacodynamic program. The diagnosis of CIU is based clinically and patients

with other causes of urticaria, which we have heard about before such as the physical urticarias, urticarias from known causes like insect sting, drugs and so on, urticarias associated with underlying disease or patients with angioedema are excluded from all of the studies.

Also important differentials which are listed in the slides are also looked at by the physician and those patients are excluded.

On entry, the patients are expected to be symptomatic so that an efficacy can be seen during the clinical trials. Typically in various studies, that has meant the patients should have a flare lasting for at least three weeks in some studies or six weeks in other studies and on entry they have symptoms lasting for two days per week or three days per week or approximately 50 percent of the days.

The patients on entry were required to have some response to antihistamine in the past and on entry they were required to have high symptoms cause. Typically, two or above on a scale of zero to three, three being higher. Medications that can confound the

disease or evaluation of the efficacy end points were excluded.

The primary efficacy variables for these urticarial studies are based on patient symptoms which are basically pruritus and hives. The symptoms in the older studies were recorded by physicians. Currently we prefer patient recording. The recordings are done either instantaneously which means how the patient felt at the time of recording or reflective which means how they felt for the previous 12 hours or so. The recordings were done either once a day or twice a day.

The typical efficacy end points has been pruritus severity, number of hives, size of largest hives on a scale of zero to three which are explained here, typically zero being less symptomatic, three being more symptomatic.

In the studies, -- secondary end points. For example, arrhythmic severity, overall condition, overall therapeutic response and so on.

A safety assessment for the antihistamines for CIU indication usually has not been a question

because the urticarial indications were secondary after the antihistamines has been studied for allergic rhinitis and the dose for allergic rhinitis and the dose for urticaria for the currently marketed newer antihistamines are the same. However, to look for disease/drug interactions in these pivotal studies, adverse events, clinical laboratory and ECGs were looked at and all the antihistamines, the newer ones on the market, are safe and effective for urticaria.

Now I would like to spend the rest of my talk talking about clinical programs. My focus again will be on Loratadine which is the point of discussion today. I will show the clinical studies and some of the results that we have. I'll very briefly touch on the design issues on the other three antihistamines and I will not show any data on these.

The Loratadine clinical program had two pivotal studies, 67 and 44. Both were placebo-controlled and one study was active-controlled. In addition, there were a couple of supporting studies. One study, 56, was a small dose-ranging study. I showed the design and results of Studies 56, 44 and

67.

The dose-ranging study, Study 56, was a small study conducted in adult patients with CIU. The study was placebo-controlled and active-controlled with one day of baseline followed by seven days of double blind treatment. The treatment arms were Loratadine 10 mg, 20 mg or 40 mg. The active treatment was hydroxyzine and there was also placebo arm.

On entry, the patients were quite symptomatic. For example, the scores for pruritus, erythema, number of hives and size of largest hives were all around two in a scale of zero to three. Here are the results for pruritus, erythema, number of hives, and size of largest hive scores. On the vertical axis, it is percentage change from baseline for all the variables. In the horizontal axis, the first three bars are the three doses of Loratadine 10 mg, 20 mg, 40 mg. The fourth bar is the active control hydroxyzine and the last bar is placebo.

As is seen from the slides, for all the efficacy end points, all doses of Loratadine were

numerically -- to placebo, was also comparable to hydroxyzine and there was no definite dose response. The company took Loratadine 10 mg dose for further development through two pivotal studies. One of the pivotal studies was Study 44. This was a seven-center U.S. study, again conducted on adult CIU patients. It was placebo-controlled with one day baseline and 28 days double-blind treatment.

On entry, the patients were again quite symptomatic with the scores being two or around two for all the end points on a scale of zero to three. The treatment was Loratadine 10 mg compared to placebo and the symptoms here were scored by investigators and a primary efficacy end point was not defined.

The four end points which I showed earlier are shown here again and on the horizontal axis now it is the weeks, weeks one, two, three and four. The small asterisks here denote significance versus placebo at a level of P4, 5 or less.

For pruritus and other scores, the active treatment, which is Loratadine 10 mg, was numerically and for most of the time statistically superior to

placebo.

The second study, Study 67, was again a seven-center study conducted in adult patients. Again, on entry the patients were symptomatic. The study had one day baseline followed by 28 days of double-blind treatment and this was an active control study. The comparator was hydroxyzine 25 mg three times a day. The primary efficacy end point in this study was measured or assessed by patients and the end point was defined as day seven change compared to baseline. This is the primary end point which is the pruritus curve. I'm showing here day seven which is week one and other time points. At the primary end point, which is the day seven, both the drugs were almost super-imposable and they were both secreted to placebo. Over time, the separation of placebo was maintained. However, hydroxyzine numerically tended to be better than Loratadine.

An important secondary end point is change in the number of hives and, again, the active treatments were -- placebo although there was no -- significant differences here.

The Loratadine clinical program that you have the medical officer review in your briefing book had two pivotal studies. The designs were very similar to the Loratadine program except that these studies lasted a bit longer, for six weeks. These two studies were adequate to support approval for these drugs for Loratadine for CIU indication. Also, there was a -- study which was pharmacodynamic study.

The Cetirizine program also had two pivotal studies. They were both placebo-controlled. One study was a fixed dose ranging study where multiple doses of Cetirizine were compared to placebo. The second study allowed for dose titration where patients were allowed to increase the dose based on physician's supervision. In addition, the two supporting studies which looked at patients who had idiopathic dry skin pruritus which was meant to indicate the patients did not necessarily have an allergic -- and these studies were not generally supportive of efficacy so Cetirizine currently has the indication of CIU like other antihistamines.

The Fexofenadine program also had two

pivotal studies. They were both four week studies and in both the studies dose effects of Fexofenadine ranging from 20 mg to 240 mg twice a day was explored. All the doses of Fexofenadine were -- to placebo and there was no dose response beyond 60 mg bid doses. Based on these two studies, Fexofenadine is currently approved for CIU.

In the prescription world right now, the newer antihistamines that have the indication for CIU symptom control are the four that I went through very briefly. These are Cetirizine, Desloratadine, Fexofenadine, and Loratadine. The indication states treatment of CIU symptoms.

The older antihistamines, which are often called first generation, also has some approvals for urticaria or urticaria-like symptoms. For example, the combination product which is antihistamines and Extendryl hydroxyzine, cyproheptadine and promethazine has indications which states, might complicate uncomplicated allergic manifestations of urticaria or angioedema or both. Specific language varies slightly for the different drugs.

Currently in the over-the-counter situation, there are no drug products that are approved for the treatment of CIU, urticaria of other forms or itching due to hives.

Based on the clinical studies submitted to the FDA for the NDA and subsequent post-marketing -- the currently available newer antihistamines are safe and effective for treatment of CIU symptoms. Of the various types of CIUs or urticaria I should call it myself, are the various types of urticaria. In the clinical trials, CIU was studied because, for reasons we explained earlier on, CIU is amenable because the patients are symptomatic and the disease -- to be studied in -- clinical trials. Generally, if antihistamine is found to be efficacious for CIU, it is possibly reflective of efficacy in urticaria for the times and in clinical practice, actually that's the way the antihistamines are used, not necessarily limited for CIU.

One has to keep in mind if H1 antihistamines are marketed OTC, they're likely to be used for all types of urticaria including acute

urticaria which may or may not be often a manifestation of anaphylactic reactions.

Thank you.

The next speaker is Doctor Ganley.

DR. CANTILENA: Actually, I think it's Doctor Holman.

DR. HOLMAN: Good morning. My name is Matthew Holman and I'm an interdisciplinary scientist in the Division of Over-the-Counter Drug Products at the FDA. Today I'll be talking about U.S. regulations, foreign marketing, and label comprehension studies conducted by the sponsor.

As indicated by the title of my talk, my talk will be divided into three sections. First, I'll talk about U.S. regulations regarding OTC antihistamines and specifically with regard to the CIU or hives indication. I will then look at a specific antihistamine, that is Loratadine, and look at its marketing around the world and then lastly I will just briefly highlight some key points to the label comprehension study conducted by the sponsor followed by a summary of my presentation.

As Doctor Chowdhury mentioned, there are two routes that a drug going OTC can go by. The first is an NDA which is product-specific and sponsor-specific. The second route is the monograph which is ingredient-specific. As Doctor Chowdhury mentioned, there are currently no approved OTC oral antihistamines with a CIU or hives indication. Therefore, I'm not going to discuss the NDA route but rather I'm going to focus on the monograph system.

The monograph system is a three step process open to the public. The first step is the advance notice of proposed rule making or the ANPR. This contains the Advisory Panel report and this is published to notify the public of the agency's intentions regarding specific ingredients and indications and is to request comments from the public.

The second step is a tentative final monograph. Based upon comments received from the ANPR, the agency publishes a TFM containing a proposed rule making and it requests comments from the public.

The last step is the final monograph.

This is again based on comments from the TFM. The agency develops final regulations regarding specific products and ingredients and publishes these. Once the final monograph is effective, any ingredient within that final monograph can be marketed without prior approval from the FDA as long as regulations are followed.

Now that I've given you a general description of the monograph process, let's look specifically at how this has to do with OTC or antihistamines. About 25 years ago, the ANPR was published and this was published for a pretty broad category of cold, cough, allergy, bronchodilator and anti-asthmatic drug products of which antihistamines were part of. Again, the Advisory Panel report was published. In that report, which again covers this entire drug category, there was no mention of CIU or hives.

A few years later, the Tentative Final Monograph was issued and, rather than describe this whole entire drug category, the Tentative Final Monograph in this case referred specifically to OTC

antihistamine drug products. In the TFM there was one comment referring to hives that requested indication of hives. However, there is no data submitted and, as I mentioned, the panel did not report on hives. Therefore, the agency declined this request.

There was a final monograph issued shortly after TFM and, again, the final monograph was specific for the OTC antihistamines. In this, there were two comments relating to CIU or hives. The first comment requested symptomatic treatment of allergic itching. This comment was subsequently withdrawn, so the agency did not respond.

The second comment referenced the literature, data in the literature that supported relief of itching skin caused by, among other things, hives. The agency did not agree with this comment based upon primarily three points. The first is that hives are a component of anaphylactic reaction. The second and related point is that the average person can not distinguish between mild and life threatening conditions with similar symptoms, i.e., hives.

And the last point was that one of the

references cited by this comment stated that the ideal treatment for urticaria was identification and removal of the cause. The agency agreed with this comment and, therefore, did not allow this indication.

Now that we've discussed a little bit about the marketing of OTC oral antihistamines within the U.S., I'd like to focus our attention outside the U.S. by focusing on the marketing of Loratadine. I'll give you a brief picture of the marketing of this drug outside the U.S. It is prescription medication in approximately 80 countries. It's prescription-free in 33 countries. However, of those 33 countries, only 29 of those countries allow a hives or CIU indication.

I'll further define this by letting you know that of those 29 countries, 22 of the countries sell this product behind the counter. That is, it has to be purchased at a pharmacy through a pharmacist. However, no prescription is required.

The other seven countries sell this drug, market this drug over the counter. Again, similar to the U.S., Loratadine can be purchased in these seven countries without a prescription, without a pharmacist

intervention from a variety of sources such as gas stations, convenience stores.

Rather than talk about all these countries, I'm going to focus just on two of those and those are Canada and the United Kingdom and hopefully give you a flavor for how this drug is marketed in these two countries and around the world.

First, let's take a look at Canada. Loratadine has been marketed in Canada since about 1990. It has always been marketed over the counter in this country, never behind the counter, and it's never required a prescription. In Canada, it's allowed two indications and those are allergic rhinitis and hives.

Now let's just take a look at again just one example of the labeling used in Canada for Loratadine. The labels I've shown here are for a 10 mg tablet. You can see on the left there's a product labeled for allergy. Again, 10 mg tablet. There's no mention on the front panel or the rear back panel of CIU or hives. However, on the right you can see that there's again, the 10 mg tablet labeled for skin itch. In this case, the front label reads, fast relief from

skin allergic conditions, bullet, skin itch, bullet, hives.

Now let's take a look at United Kingdom. In the United Kingdom, Loratadine was initially marketed in the pharmacy class. This corresponds to behind the counter meaning a prescription was not required but it had to be purchased through the pharmacist. However, about four months ago in December, Loratadine was switched to general sales list. This again equates to OTC meaning that it can now be purchased directly by consumers without a pharmacist intervention.

Just an interesting note that in the United Kingdom, once the switch to GSL was made, the packaging was limited to seven tablets or a seven day supply. Again, like Canada, the two indications are allergic rhinitis and hives.

The last point I'd like to make is that in the United Kingdom there's only one other oral antihistamine which is on the GSL list and that is Ceterizine and, again, this was switched back in December. Again, I'd like to just show you an example

of some of the labeling in United Kingdom. This label here is labeled allergy tablets for hay fever or other allergies. I've blown up a statement on the back panel that refers to hives or CIU and that reads, "Claritin Allergy may also be taken for allergic skin conditions including rash, itching and urticaria (hives)."

Now that I've talked a little bit about these two countries, I'd like to step back and sort of summarize the labeling around the world. Rather than look at all 29 prescription-free countries, we reviewed labelings from 19 of these countries including six of the seven OTC countries. I've sort of just summarized the labeling and references to CIU or hives in these countries.

Only one of the 19 countries was CIU completely indicated on the label and that label read, "Chronic urticaria of an unknown source." However, in 12 countries the label read simply "Chronic urticaria or chronic hives." It did not mention the source of the hives." Further, there were three more countries that simply listed urticaria or hives and another

three countries which combined urticaria with a broader term of allergic skin condition.

I'd like to make one last point and that is that of these 19 countries, not a single country indicated that the consumer should be diagnosed by a physician prior to using this product. Actually, I'd like to pause just one more minute to sort of put this into context by telling you that of all these statements that I just described, less than half of those statements were on the carton labeling. Rather, the majority of these statements were on the package insert meaning that consumers could not read these indications at the time of purchase.

And now let's just take a look at the label proposed by the sponsor. Again, I'm just looking here at the 10 mg tablet. You can see that this package is labeled on the front for recurring hives. It says it "relieves and reduces itching and rash due to recurring or chronic hives." Again, I've blown up a statement on the back panel from the uses section of the drug facts label. There's two bullets. The first bullet refers to CIU and it reads "relieves

and reduces itching and rash due to recurring or chronic hives of an unknown source."

The second bullet, which is in bold font, indicates that the consumer should be diagnosed by a physician and it reads "Use only after being told by a doctor that you have recurring or chronic hives (chronic idiopathic urticaria).

And similar to Canada, the 10 mg tablet also has a second carton labeling. This time it is labeled for allergy. However, it does refer to CIUs. It says "Non-sedating relief of itching and rash due to recurring or chronic hives." And again on the rear panel, the same two statements, just this time combined into one bullet and again the second statement referring consumers to be diagnosed by a doctor is in bold font.

And now I'll just briefly summarize just a few points from the label comprehension study conducted by the sponsor. The label comprehension study consisted of 565 subjects divided into five cohorts. The first cohort was self-recognized CIU sufferers. These were participants who had claimed to

be diagnosed previously by a physician as having CIU. The second and third cohort were the general population and the low literacy group.

The fourth cohort was that they had a contraindication on the labeling. These were subjects who were pregnant or nursing or who had liver or kidney disease. And then fifth cohort were the acute hive sufferers. These were subjects who had previously had hives or currently had hives but had never been diagnosed by a physician as having CIU.

For the label comprehension study, all those subjects were allowed to look at labeling similar to that which I have just shown you proposed by the sponsor and then respond to a series of questions. I'm just going to highlight a few of the questions and the responses, again to try to give you a flavor for the type of responses we saw in the label comprehension study.

The first question was an open-ended question that read, "Based on the label, what is this product used for?" Approximately two-thirds of the participants answered this question correctly or

acceptably. To answer this correctly or acceptably, the respondents had to say that the product was used for CIU. However, they could also say that it was used for another appropriate indication such as allergic rhinitis.

Of the third of the respondents who got this answer incorrect, nearly all of them simply mentioned hives as the indication, did not mention the chronic nature of the hives or the source of the hives.

I'd also like to just point out a couple of other potentially concerning responses that were seen, and that is that some subjects believed that this product could be used if you had trouble speaking or swallowing, drooling, food or medication allergy, had a fever or had breathing problems.

The second and final question which I'm going to discuss from the label comprehension study was a close-ended question similar to the first. It read, "Is this product intended to be used for the following conditions?" with a list of 10 indications following this question. I'm not going to talk about

all 10 indications but instead going to focus on just three. In this table, the columns here represent the five cohorts and then this far left column here represents the total of all five cohorts combined. These percentages, I should point out, represent the percentage of respondents who believe this was a correct indication for the product.

The first indication or recurring or chronic hives of an unknown source. That is, CIU. And you can see that nearly all the respondents correctly identified this as an indication for the product. However, the second indication, food allergies which is incorrect, a little over 10 percent of the respondents believed this was an appropriate indication for the product. Moreover, if you focus on the acute hives sufferers here at the far right of the table, you can see that number is almost double.

And then lastly, a one time outbreak of hives, i.e., acute hives. You can see that about a third of the respondents believe this product could be used for a one time outbreak of hives. Moreover, if you ignore the first cohort of CIU sufferers who have

been diagnosed by a physician as having CIU, that number is basically double. Excuse me, not double. But about 40 percent of the respondents in the other four cohorts believe they could use this product for a one time outbreak of hives.

And then lastly I'd just like to mention the self-selection portion of this study and that consisted of the following question. "Considering everything on the package label, is this product intended for you personally to take home and start using?" There were three possible responses that the participants could give to this question. The first is yes, I can take this product. The second is I can only take this product after asking a doctor and third, no, I should not use this product.

Again, I've summarized the results in a table here and you can see in the first cohort the CIU sufferers, 100 percent of that cohort got this answer correct and that is because all three responses were considered correct or acceptable for this cohort. However, if you look to the far right, the acute hives sufferer, you can see that just over 50 percent of the

respondents got this correct meaning that nearly 50 percent of acute hives sufferers believed they could use this product without asking a physician first.

And then lastly, I'd just like to provide you with the take-home points and those are this. OTC or antihistamines can not be marketed currently for CIU or hives under the monograph system. The second. Chronic hives was the most common indication on the labeling from around the world and also Loratadine typically is marketed prescription or behind the counter. That is, it's not typically marketed as over-the-counter outside the U.S.

And then lastly, it seems obvious from the consumer study conducted by the sponsor that consumers will use this product for all types of hives.

Now I'd like to introduce Doctor Ganley.

DR. GANLEY: Okay. What I'm going to just do in the next five minutes or so is just give a quick overview to highlight some of the issues. I think that just hearing the questions after the sponsors' presentations, you sort of get the idea where the issues are. So this may be somewhat redundant.

What I've listed here are safety criteria for OTC drugs, and these are actually taken from our regulations. There's probably additional thoughts that could be captured in these, but there should be a low incidence of adverse reactions or significant side effects under adequate directions for use. The key words here are "adequate directions for use and the incidence of adverse reactions." There should also be warnings against unsafe use and there should be low potential for harm which may result from abuse under conditions of wide-spread availability.

I think inherent in this is that a product in the over-the-counter market can be accurately selected and deselected by the general population and not just a subset or a cohort of that population. I don't include a slide regarding the efficacy of this product and I'm somewhat remiss in that after hearing Doctor Chowdhury's talk where we talked about efficacy. One of the reasons for doing that is that if the committee decides that urticaria or hives is an acceptable OTC indication but it should be for the general population, that would include a population

that would include acute hives, does the efficacy data that sponsor have on hand support the treatment of acute hives? So that would be one of the issues that you would have to also address.

These are just some observations that I just want to make clear. First with regard to the FDA position on urticaria as an OT indication. We don't really have a position. Many of our reviews, although somewhat critical of some of the things the sponsor has done, is not an indication of our position on this. We really are depending on the committee providing some insight on whether this should be an OTC claim and also specifically whether the application at hand is acceptable.

The other thing, which has been recounted earlier, is urticaria or hives as an OTC indication in other countries. We also have to recognize that pharmaceutical marketing in other countries is different. Consumer behavior is somewhat different in some cases and pharmacy practices vary among countries. Clearly, the fact that the OTC-ness of this in other countries is based on having some type

of health care provider or pharmacist be the one distributing the medication.

The last thing that we really I think are in agreement with the sponsor is consumers may be already using OTC antihistamines for urticaria. Some of the data they provide actually indicates that. It would be interesting to understand how does that happen? Why is that so? Consumers can be influenced by various information resources. The Internet is a prime example. You could go into the Internet and do a search for urticaria and it quickly takes you to resources where it tells you how to treat urticaria.

The other thing that we don't really have a good understanding of is how these products are marketed. One example would be the brand names. There's many brand names out there that include the term allergy. How do consumers interpret that? Do they extrapolate a lot of different diseases and illnesses?

As far as urticaria or hives as an OTC use, one of the important things to understand is for acute or chronic hives, what is the frequency and

significance of associated conditions? Some of those were touched on this morning as far as angioedema and anaphylaxis. I've heard the term rare and infrequent. It's hard to really get an understanding of what that actually means, especially when you have a product that would go OTC and be available to tens of millions or hundreds of millions of people. Things that are rare in one setting may become a little more common in another setting in terms of the distribution.

Clearly, the consequences leading to serious adverse outcomes are important to understand here. I think, just hearing the discussion of the committee with the sponsor's presentation, they touched on some of those issues.

Also, what's important is the condition is misdiagnosed by the consumer as urticaria. They were discussed also earlier. Physician intervention. When is it necessary? Delay in seeking physician advice are important issues that need to be better understood or discussed, I guess. Consumer behavior. Will the OTC availability encourage self-treatment without

diagnosis for chronic urticaria? Now if you have a product out there that is marketed for that, will consumers have less of a tendency to go see a health provider and, if they do, was there a negative consequence to that?

Consumer self-diagnosis condition. Clearly, I think a chronic idiopathic urticaria population who goes to a physician and is given that diagnosis, I could believe that they would be able to diagnose that condition should it occur again. I'm not sure I need a study to tel me that. But I guess the issue comes down to what will the general population do with that and what things can we do to influence behavior because the bottom line here really is to reduce risk and how can we manage risk here in a prospective way?

As far as the sponsor's proposal, as you've heard, they've wanted to limit the indication to chronic idiopathic urticaria by a physician. In support of that, they've submitted surveys and label comprehension. I reviewed the surveys and wrote the review and I'm not going to go over all the details

again. The important things were, in my view, that I'm not surprised by the results of the study. If you go to any population that has a disease that has intermittent symptoms and they've gone to a health care provider who is treating them with some medication and ask them to take that medication when the symptoms recur, I think most people are capable of doing that. So the outcome that a CIU population could actually use this medication is just not really that surprising.

As far as the consumer survey, I had some critique about the multiple choice questions being used and open-ended. The sponsor addressed that. I don't see a need for me to address that again. Most of those individuals in that survey had used oral antihistamines prior to getting a physician's diagnosis and I think that's likely to continue in the future.

One other thing is that chronic idiopathic urticaria is not a commonly used term, particularly in telling an individual what the diagnosis is.

The sponsor proposed to limit this

indication by simply having labeling that states, use only after being told by a doctor that you have recurring or chronic hives of an unknown source, chronic idiopathic urticaria. As I mentioned, we have had some experience with that. Not all of it has been great. The vaginal anti-fungal products have a warning that says do not use if you have never had a vaginal yeast infection diagnosed by a doctor. Subsequent studies have suggested that as many as 40 percent of individuals that use those products have never had that diagnosis.

So the problems with the sponsor's approach is that the product is likely to be used for any type of urticaria. Twenty to 25 percent of subjects who experience hives have chronic hives. That means 75 to 80 percent of a population would have-- there'd be more people that use that have acute hives than would have chronic hives that would have access to this product.

There was no data provided to demonstrate accurate self-selection and de-selection in a general population, not just a CIU population. There is no

consensus for consumers on the name CIU. Hives is likely to be translated broadly by the consumer. The labeling restriction proposed by the sponsor will not likely limit use to CIU subjects.

So the issue for the committee is whether urticaria should be an OTC claim in any form. If the committee decides that the answer is no to that, that means there is just no studies or anything that the sponsor can do that would ever provide sufficient information for that to be an OTC claim. So if you come to that conclusion, the meeting is going to end early today.

The second part would be if you believe that it's a possible claim, whether the data submitted by the sponsor is adequate or whether there is other data that they need to collect and provide.

With that, I'll conclude my discussion.

DR. CANTILENA: Okay. Thank you, Doctor Ganley and other members of the FDA team for their presentations.

We now have time slotted for questions to the FDA presenters. We'll just sort of use our open

format that we used earlier. Doctor D'Agostino.

DR. D'AGOSTINO: The question is probably to Doctor Holman but maybe Chowdhury would also be appropriate. You presented that the drug is used in a number of non-U.S.A. countries and the actual indication does say hives. Is there a body of data? I mean I realize that the FDA does its own reviews and so forth, but is there a body of data, publications and what have you, where the drug has been effective, proven to be effective or substantial evidence that it is effective? Also, we keep hearing over and over again that the field thinks it is. What are they basing this decision that it is appropriate on? What database do we actually have? I'm not talking about the Rx. I'm talking about the OTC aspect of it.

DR. CHOWDHURY: Yes. Let me give you the answer from the prescription standpoint and then I'll ask Doctor Holman to answer the question, too. In response to your question, the studies in-house that we have reviewed for the antihistamines are for t CIU indication and I'm not aware of any data that we have that looks at the efficacy for other types of

urticaria.

DR. D'AGOSTINO: There are a substantial number of countries where the indication is high. You said it's OTC. What's the database?

DR. HOLMAN: I'm not really sure exactly what the database is. I talked to some of my counterparts in Canada and the U.K. and there are regulatory bodies there. We never really discussed the database. I think it was just sort of assumed that because they were effective for CIU, they would be effective for hives. All they indicated when I specifically addressed the question, is this a hives indication or is this a CIU indication, they indicated that it was a hives indication because they did not feel the consumers would understand the term CIU or any statement referring to CIU.

DR. D'AGOSTINO: Why is the field so convinced that it is appropriate treatment?

DR. HOLMAN: I think, as Doctor Wilkin and Doctor Monroe mentioned, the pathway seems to be common between whether it's chronic or acute urticaria, seems to be a common pathway, and that is

the release of histamines. Therefore, antihistamines are effective in preventing CIU or treating CIU would be effective at treating really a more broad hives or urticaria.

DR. D'AGOSTINO: i'll get off but I just want to understand. We're saying we don't think that there's a database for hives.

DR. HOLMAN: No, there's none that I'm aware of. I think again, as mentioned earlier, it's just an ability to conduct the study to determine that.

DR. D'AGOSTINO: Thank you.

DR. CHOWDHURY: In response to your question, I would probably also ask Schering to see if they have any data in hives of other types because they have two of the four antihistamines that has a CIU indication in the U.S.

DR. CLAYTON: We do not have any clinical data on acute hives. I think, back to Doctor Wilkin's presentation, the mechanism of action is the same and it is still the first line therapy for acute hives, as was in his presentation. But no clinical data that

I'm aware of.

DR. CANTILENA: Other questions, Doctor Szefler.

DR. SZEFLER: This is perhaps for Doctor Chowdhury. As I looked at the literature, and it's not an area that I look at intensively, but as I tried to look at it, I tried to understands what are the pharmacodynamics of the effects of the antihistamines and does it reduce the course of episodes? Does it just merely reduce the itching? If it just merely reduces the itching, then how does that differ from acute hives where that would be the main purpose would be to reduce the itching? So I'm trying to kind of sort out the dynamics in terms of time-related effects, magnitude of effects. Statistically it's there in a lot of these parameters, but I'd kind of like to get a feeling of what you would select as a primary outcome variable if you had to look at this area.

DR. WILKIN: I can speak to that. Basically, it's a symptomatic kind of therapy. If you want to think of it as the where is the disease, if

it's the IGE mediated, it's the B-cells, the -- arm of the immune system recognizing something that really doesn't pose that much of a threat to the body being recognized as foreign and then being over-reacted to by the production of IGE that will bind to the mast cell. That's probably the disease part. Where the histamine is downstream from the mast cell, how the antihistamines work is they just work for that particular episode but they don't have any effect on long-term prognosis over the course of the disease. Sometimes patients will have IGE and later they'll develop IGG blocking antibodies are sort of things that they'll have a natural tolerance develop, but that's not because they were on the antihistamine therapy. Antihistamine therapy is symptomatic. It blocks the histamine receptors that mediate the itch and also the vasodilation and the vascular permeability.

DR. SZEFLER: Let me just tease it out a little bit more. Is this something that -- again, when I was looking at the pharmacodynamics, there weren't diagrams jumping out. There were tables in

terms of durations. is this something that you expect to see at 12 hours a statistical difference, 24 hours? There's not a lot of literature and the literature is not kind of crystal clear in terms of these effects. I'm trying to look at how do you look at it in terms of if you were to look at acute urticaria, what could you see and what would be the primary outcomes that you could measure and look at?

DR. WILKIN: Well, acute urticaria, although it gives the picture of a single episode where one breaks out and the hives are there for maybe 24 - 36 hours, something like that. In point of fact, the hives migrate around so it's mast cells releasing the mediators in different portions of the skin at different times. If at the beginning of one of those episodes one takes the antihistamines, you can actually then shorten the particular course. Does that speak to the question?

DR. SZEFLER: Yes. i'm trying to decide in my own mind whether this is an area that's been poorly studied because there's been just not enough direction and there's been so much assumption there,

we don't have to study this in depth and it's really not been looked at as a discipline the same as, say, things like asthma have been looked at and defining primary outcomes and getting a real good -- area because what I get the impression of is that well, it's a tough area to study and it's kind of hopeless and maybe we shouldn't go for acute urticaria but then, on the other hand, maybe the incentive has not been there to come up with clever methods to really look at this in depth.

DR. WILKIN: I think you've actually touched on the real piece and that's the methodology. How does one actually look at acute urticaria? You would almost need to be clairvoyant to know who's going to get acute urticaria to capture them in time to give them a medication so that you could follow them for what very often is just a couple of days of an acute urticaria episode. I mean we talk about the six week point being the time where we then will define it as chronic urticaria but most of the patients who have acute urticaria don't have six weeks worth of acute urticaria. That time point is just

simply to separate those who have the bad prognosis. It's very likely theirs is not going to go away. Most urticaria goes away in the first couple of days or the first week. So it would be very difficult to recruit patients, study them, give them drug or give them placebo and make the comparisons because there's going to be a high spontaneous disappearance of the urticaria during that time period. I think acute urticaria is just incredibly difficult to study.

Now, what you can say about acute urticaria and chronic urticaria, many of the etiologies if you will, the things that ultimately are outside of the mast cell that then impact on the mast cell, many of those are in common. The mast cell only has one trick. It's got the same little vesical filled with all of these things that it releases. It is an identical vesical, regardless of what the difference etiologies, be they immunologic or direct mast cell media release, it still releases that same vesical which still has the same effects on the vasculature and the afferent nerve endings.

So I do think that it's not data. It's

going from first principles but I think it's acceptable to approach urticaria as being very homogeneous in its final terminal pathways unless you've got one of the mechanisms that we know about, one of the compliment deficiencies or other sorts of things that it's a special variety and there are some findings that could, I think, be crafted into labeling that would alert patients about the additional associated features or the notion that the urticaria doesn't itch.

DR. SZEFLER: I guess, again, I kind of wonder just how much time has been spent in terms of trying to come up with studies because I recall one of the slides that said food is a precipitant in about 10 percent of the patients and you could challenge patients as long as you didn't think that this would cause anaphylaxis if that wasn't a component so you could time the challenge. As long as you looked at what was your primary outcome variable, I think you could measure in a suitable enough population whether there was an effect on this kind of parameter. So again, I'm just kind of wondering how much. Maybe

it's been assumed that because the sedating antihistamines work in these areas that it's not an area of concentrated studies. But I think I could sit back and design studies on this. As long as you had some feel from the literature what were primary outcome variables, what would you measure.

DR. CANTILENA: Actually, I think some of these issues will come up this afternoon, if we can hold that, because then we have Doctor Wood, Doctor Davidoff and Doctor Sachs next.

DR. WOOD: I have two questions. I'd like to ask them separately because they're sort of unrelated. I guess I'd like to address them to Lloyd and Doctor Rosenberg. As I hear this, it seems to me that as we try to put it together, we're hearing evidence that the drugs are effective in the treatment of CIU and the worry seems to be that patients with other types or urticaria and potentially other skin diseases will use this therapy.

So my question to the dermatologists is should I care about that? I mean does that really matter if other patients use it because if it doesn't,

then these other issues that are kind of just bubbling up here and, although they're interesting, they're not really relevant to the decision on the table.

So the question I'm really putting to you is there bad things that are going to happen to patients who have other skin diseases and, apart from delay, who might take this acute urticaria or for other diseases or whatever?

DR. ROSENBERG: I would say no based on long experience and being in dermatology for a long time. Also, I'll ask the chairman about this afternoon's meeting. Have the Academy of Dermatology, the Allergy Society, sent people here and request a place on this meeting?

DR. CANTILENA: No, it actually doesn't look like that. We only have three individuals who have registered for this afternoon.

DR. ROSENBERG: I think that answers your question, Doctor Wood, like the dog that didn't bark. I've been involved in these proceedings when we talked about Acutane and the pediatricians were here in force and when some of us were trying to have over-

the-counter hydrocortisone made a legal prescription in this country, the Academy of Dermatology expressed at that time grave reservations about the safety of things being missed and it just went on and on over many, many meetings. I think that those bodies all pay close attention to what goes on at FDA and would have sent somebody here had they raised any issues at all.

DR. KING: I have to agree, having been on the Acutane study in which everybody got on a campaign about all the regulations that should be in place. It is a dog that didn't bark. Many of the folks we see come in and we have them fill out lots of sheets about what they've done. They know more about Benedryl sometimes than our residents do. So I think they're going to be taking it because mama, the neighbors, particularly people who are English as a second language are going to take it anyway. I can't remember a case in which taking a first or second generation antihistamine blocked or in any way endangered a patient from taking it prior to coming to see a dermatologist or other physician.

DR. WOOD: So the answer to that is thaI shouldn't care.

DR. KING: Shouldn't care.

DR. WOOD: The second question I have is a sort of question from a simple guy in Tennessee. I'm interested in the labeling idea, that you should only take the drug if you've been told by a physician that you have chronic idiopathic urticaria, but just in the patients I see in Tennessee, I don't think many of them leave our hospital saying to themselves as they walk out the door, I've got chronic idiopathic urticaria. That doesn't sound like a phrase that drops off the lips of the average patient somehow.

So I wonder if that's the right label and if there's something that's more commonly used by lay people and this gets back to the question of the hives. That seems to me something that people would use more commonly. I just worry about demanding a label be given to something that patients don't customarily use, certainly not my patients. Maybe other people, the sophisticated people in the northeast. Lloyd, what's you feeling about that?

DR. KING: Well, actually I'm biased because I'm from Tennessee, too. Is there anyone here who's not from Tennessee? Well, there are several. We have had notoriety because of Vice President Gore. I think the issue as I thought about it is if we're going to have across the world, you almost have an issue of labeling which is what do you do about groups of people in which English is a second language or conversely in which French or Russian is a second language, so to speak. You really have to talk about the issues of access to drugs which potentially can hurt you and what percentage of those people will be hurt. Having worked for cause of orphan drugs, one percent of a huge number is still a huge number. And so I think the issue would be how many people would actually be hurt if we just put chronic hives on the label. I suspect it wouldn't be that many in any case and so if you had to put on there that for aspirin it can trigger fatal reactions, it almost did my mother times two, you could get into a labeling nightmare. So I would have no trouble putting on there indicated for chronic hives, see your doctor, and I'd like to

see something like a big eye ball and MD or its equivalent and then whatever language saying see your doctor if there's --

DR. WOOD: In my mind, it would seem like insisting that patients with a diagnosis of acute myocardial infarction rather than a heart attack which for most patients is what they're really going to carry in their conversation. So both of these seem to circle back to the conclusion that if we are not worried about patients taking the drug for other types of hives because of risk to them and, in addition, the vernacular that patients use is hives rather than chronic idiopathic urticaria, then that seems to me to answer some of the other issues that are on the table which are more scientifically interesting perhaps but are not practically enforceable. Is that fair?

DR. KING: I agree. I think if you have, as I often times approach a Palm Pilot or some of these PDA kind of things, if you don't know how to use it or you don't understand that, I'd rather have something straightforward, chronic hives as opposed to see your doctor if you have chronic hives of

undetermined etiology. I like your thought.

DR. CANTILENA: Doctor Davidoff and Sachs, then Gilliam.

DR. DAVIDOFF: Yes. I have a question primarily for Doctor Chowdhury. Others may want to comment. It has to do with the efficacy data because, even though I realize, as I understand, the OTC decisions rest primarily on issues of safety, it's really more, I think, a balance of safety and efficacy because even if a drug is not very toxic, if it's ineffective, that's not a very good equation. Which raises the question about how to interpret the data on efficacy in CIU. The data that were presented there, comparing the non-sedating antihistamines to placebo are really, as was commented on in the materials provided, fairly under-whelming. The difference is, I guess, about a mean of half a point on a four point scale. But beyond that, there were no confidence intervals, so I don't know how to interpret that since I don't know what the possible range of quote "true" effects was or wasn't.

But underlying all of that is the question

of well, even accepting .5 on a scale of total of four, that may be statistically significant, which I guess it was, but is that clinically significant or maybe others could comment on what is felt to be clinically significant? To help with that, it would help to know the distribution of responses because it could be that a substantial portion of the patients so treated really got very strikingly positive responses but it might be sort of a bell shaped curve. Maybe you could elaborate a bit on the meaning of significance here.

DR. CHOWDHURY: Well, this is a very difficult question to answer what is a clinically meaningful difference versus a statistically significant difference and for evidence of efficacy we compare to placebo and if the drug is statistically significantly superior in situations like this where we did not really have a prior understanding what difference is clinically meaningful. The differences, as you saw, in the urticaria trials were not that remarkable. Really, for antihistamines, were there indications also like allergic rhinitis. The

differences from placebo are usually not that remarkable. And also there is a significant -- not statistically so but just numerically a placebo response there for the two arms as the time goes on comes closer and closer.

So it's very difficult really to put a number on that that kind of difference would be clinically meaningful. We don't have that, and the data, as you correctly pointed out, are from CIU patients and how that translates to acute urticaria is not known. As Doctor Szefler mentioned, those studies are not done, not necessarily that it can not be done. It has just not been approached, not been done. Perhaps one could design clever studies to answer these questions.

DR. DAVIDOFF: I understand about the later data on acute hives, but do you have any information on what the distribution of responses is within the study population?

DR. CHOWDHURY: I don't have it right on top of my head here and I would ask Schering to see if they can share some of the data that they have from

their studies. I do not.

DR. CANTILENA: Doctor Temple might have that somewhere.

DR. TEMPLE: I only want to point out that the same questions arise in studies of angiolytics, antidepressants and things like that. If you look at the mean difference from placebo, it's relatively small compared to the spontaneous improvement in the untreated placebo group and we don't really know whether that's a condition of the study. For example, with respect to allergic rhinitis, if you do so-called field studies, the differences are small, hard to detect. Most trials fail. If you do chamber studies where you control the antigen and introduce it, it's very easy to show effects and dose response and all that kind of thing.

Nobody quite knows whether this is a phenomenon of the study or is really true because people certainly have the impression that they have visible effects from antihistamines and yet if you look at the study results, the results are puny. So as was said, we consider it quite remarkable if you

can actually beat placebo in these settings. We have in a number of cases tried to look at the distribution of responses. It turns out if the median effect is tiny, the distribution of responses isn't very different either as a rule. There could be exceptions to that, I suppose, and we always look for tails on the thing. But that on the whole has been remarkably unproductive. So that's unsatisfactory in some ways but that does seem to be how a lot of these turn out.

DR. CANTILENA: Okay. Thank you, Doctor Temple.

Doctor Sachs and then Doctor Gilliam.

DR. SACHS: In the past we have been presented with actual use studies of the drug kind of as it would be given OTC and I was just wondering if that was not going to be done this time, #1. #2, sine we met in May, has the FDA received any more of the indicators, for example, from Poison Control or overdose or things like that which we usually look at in having the drugs go OTC.

DR. CANTILENA: Doctor Ganley.

DR. GANLEY: As far as an actual use

study, that was the determination of the sponsor that they didn't need a study. We didn't have many discussions with them before they submitted their application to even discuss that. So that would need to be addressed by the sponsor. Quite frankly, I think an actual use study in a general population to look at hives is probably a tough study to do because you can imagine if you have a population that you're actually trying to look at acute hives, how frequently does that occur and how many people would you have to actually enroll in a study like that over how many month period of time to follow up to just get 200 events of hives and did they use it correctly. You may be talking thousands or tens of thousands of people to be followed for several months. So that's one of the issues that you would have to discuss today is whether an actual use study is the best mechanism if you needed additional information or other alternative mechanisms to address that.

I don't believe we have more data. Doctor Chowdhury may be able to address that as far as the Poison Control information. The company had submitted

some data regarding the safety of the drug and I don't believe there were many cases, particularly in reports reported to them and the agency with regard to people using it for a hives indication or chronic idiopathic urticaria indication where they ran into a lot of problems. There were a few serious cases, and I think we have someone here who could address those if you have questions regarding that.

MR. LEE: I'm Charles Lee, medical reviewer in Division of Pulmonary Allergy Drug Products.

As far as the overdose information, there didn't appear to be any signal in the data that the sponsor submitted. There did seem to be a difference, however, in the proportion of serious adverse events that were due to anaphylaxis in patients who had so to speak CIU as compared with patients who had allergic rhinitis. In the initial submission, 11 percent of serious adverse events were for -- how do I want to say this? Of patients with CIU who had anaphylaxis, there were 11 percent of the entire population of patients who had serious adverse events as compared with two percent of patients with allergic rhinitis.

Probably saying to say it more clearly, the proportion of patients with serous adverse events due to anaphylaxis was higher in patients who had so to speak CIU compared with patients who had allergic rhinitis. If one looks at those reports, most of those patients, in fact, did not have CIU. Only one of those patients had CIU. The others were actually patients who had urticaria for other reasons. So I think what that kind of may suggest is that perhaps there is a little bit of a difference in the risk profile in patients who will be taking the product urticaria as compared to the population that would take it for allergic rhinitis.

DR. WOOD: Is that what you're saying or that more patients had anaphylaxis and were confused in the situation? I mean I'm not understanding, I guess, what you're saying. I would not interpret that to imply that more patients developed anaphylaxis due to the drug in that group than patients who were treating for allergic rhinitis rather than there was more of a background of an anaphylaxis that was mistakenly being treated. Have I got that wrong?

DR. GANLEY: Yes. I think that's what he meant is that if there's an increased frequency of anaphylaxis in the urticaria population to begin with, then you would expect potentially to see a difference in the percentage comparing allergic rhinitis versus the urticaria population. I think that gets back to one of the issues that I raised in my summary is what is the frequency of these events. Are they of a high enough frequency that we should have cause for concern or is it something that should be addressed in labeling or how do you handle that situation?

There was clearly, I think, one case and Charlie can clarify it was the case, of a person who had an allergy to shrimp, I believe.

MR. LEE: Right. The one fatality due to anaphylaxis was in a seafood allergic patient or seafood sensitive patient who apparently chose to ingest a pizza with the seafood removed from the pizza apparently developed urticaria, early symptoms of anaphylaxis, took the product in what appears to be an attempt to treat the symptoms and who eventually died from the anaphylaxis. It's one single case. However,

I think that in conjunction with what Doctor Holman had on his slide with 16 percent of the general population believing that the product is intended for food allergy, I think it does raise some concerns about potential misuse of the product in patients who had inappropriately selected, particularly if one takes into account that that population making that inappropriate choice, when you throw in, say for instance, a direct to consumer advertising, how patients perceive advertising, if that in fact might increase the risk of that happening or increase the likelihood of increasing the percentage of patients that might make a poor choice like that.

DR. CANTILENA: Okay. Well, thank you. Some of those issues I'm sure will come up this afternoon and then our final question for this morning would be with Doctor Gilliam.

DR. GILLIAM: I was wondering if the FDA or maybe Doctor Monroe knows. What's the incidence of CIU in general or of hives in general and what made me think of this was the package insert that was going around. I'm a little concerned that they're going to

come out with separate packaging just for CIU. It would make me much comfortable if it was on the box with allergy indication. Also, I just see this as being maybe them using this to make a whole other market for something that's not really a big issue and if somebody could shed some light on that.

DR. CANTILENA: Charlie, do you want to try that one?

DR. GANLEY: Well, I think in our executive summary we sort of threw that in as an issue for how do you market and what is the -- you know, you look at these numbers and it's hard to get a sense of how many patients per year have hives I think is really what you're asking because a lot of the percentages that are provided is the cumulative prevalence over time. The issue really comes down to well, are there 10 million cases of hives in the United States each year and 20 percent of those are chronic and 80 percent are acute or something related to that. That's I think what you're asking and I think that's an important question to understand. I don't know what the answer is because most of the

figures I've seen are cumulative prevalence over a lifetime.

DR. CANTILENA: Is there anyone from the sponsor who would like to add to that?

DR. MONROE: I would agree. As we said, about 15 to 20 percent of the population experiences urticaria and only about up to three percent of those in their lifetime have chronic idiopathic urticaria but at one point in time what the incidence is, I'm not aware.

DR. GILLIAM: My question is is there really an indication for CIU if the prevalence of this is so small, is it really needed?

DR. CANTILENA: Well, I think probably the answer is obvious if you ask the sponsor because that's why they're here. So maybe on that note we will break for lunch and actually if you wouldn't mind, can we come back at 1:15. We'll go an extra 15 minutes. We'll have the public comment session start at 1:15. Thank you.

(Whereupon, off the record at 12:07 p.m. to reconvene at 1:15 p.m.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(1:19 p.m.)

DR. CANTILENA: I have just one carryover from this morning's question and answer session of Dr. Clayton, I believe, would like to share with us some information that was in response to a question from Dr. Uden. They have some information that they would like to show us.

Do you have that, Dr. Clayton or Mr. Neuman?

DR. CLAYTON: Mr. Neuman.

MR. NEUMAN: This was in regard to the question on the race regarding the label comprehension study. I had the wrong chart when we spoke. The African American population in that study was significantly larger than what I had portrayed it to be. It was 20 percent in total.

In the CIU population it was 10, in the general population it was 22 percent, 52 percent of the low literacy group, and 20 percent of the special population, and 11 percent of the acute hives cohort.

DR. UDEN: And do you have Hispanic

information from Dr. Gilliam?

MR. NEUMAN: Yes. The Hispanic population was 5 percent over all. It was largest in the low literacy cohort where it was 10 percent.

DR. UDEN: Okay. So 65 percent of the low literacy group were African American and Hispanic?

MR. NEUMAN: That is correct. 62 percent actually.

DR. UDEN: Thank you.

DR. CANTILENA: Okay. Thank you for that information.

We'll now move to the public comment section of the agenda. We have three speakers. Each speaker is reminded that they have five minutes for their entire talk. Our first speaker will be Dr. Gary Kay.

DR. KAY: Good afternoon, Dr. Cantilena, and members of the committee, I'm Gary Kay. I'm the Associate Clinical Professor of Neurology. I'm a Neuropsychologist from Georgetown and also Director of the Washington Neuropsychological Institute. By means of disclosure, nobody has sponsored my trip. I live

here in Bethesda so it wouldn't be much sponsorship anyway.

Other than that, with respect to financial support I have received grant and research contracts support from Schering-Plough and from Aventis Pharmaceutical in the area of antihistamines. I've been a consultant to Schering and to UCB in the area of antihistamines in the past.

My comments are on chronic idiopathic urticaria and considerations related to quality of life and to CNS issues. First of all, I think it hasn't been really brought out today in our discussions of CIU the impact this has on patients besides the symptoms of their rash, the amount of itch and scratch and all this.

These patients really suffer a great deal of distress and discomfort. One of the most prominent quality of life impacts are on their sleep. These patients report very disturbed sleep. Also there is the social embarrassment. The disruption of sleep is probably due to a combination of the disease and the treatment that is often used, the sedating

antihistamine treatment for the chronic idiopathic urticaria.

Running a simple Medline search typing in the words chronic idiopathic urticaria in combination with any of the OTC antihistamines like diphenhydramine, chlorpheniramine, triproladine (phonetic). If you run that, you are going to find about 24 current articles in there about efficacy and use of the over-the-counter sedating antihistamines for chronic idiopathic urticaria.

Run the same search with the words again chronic idiopathic urticaria, loratadine, desloratadine, fexofenadine, cetirizine, and you get a list of 67 current studies on efficacy.

Obviously these medications are widely used. There's a lot of description in these articles, especially review articles, that this is a mainstay of treatment for chronic idiopathic urticaria.

Well, I think we all have to recognize we're talking about risks of medications. All of the current over-the-counter antihistamines used for treatment of CIU carry a precautionary statement, "May

cause drowsiness. Use caution when driving or operating dangerous machinery."

Obviously you have concerns about people reading labels and following labels and how seriously do they consider those labels. I would just suggest that you take a look at the findings from the hearing that was held for the FDA NTSB hearing in November, the hearings on sedation and impairment, to take a look at particular issue. We are not going to recover that again today.

The fact is that if you look at the studies I mentioned, those 24 studies where they review the adverse events in those chronic idiopathic urticaria trials, the most common AEs that are found in those studies is sedation in combination with those medications.

Another issue in CIU is that there's an attitude among many of the physicians that one of the things they are going to do to treat this patient is to help them sleep at night and so administer to them a sedating antihistamine at bedtime. That may help them with the scratch and the itch and may help them

because they've been complaining of not sleeping well at night but, in fact, that may not be so recommended.

Still, you are going to find if you look in the current literature even references to AM and PM dosing. Treat the patient with a sedating antihistamine at bedtime and give them a non-sedating antihistamine in the morning so they won't have a sedating effect.

The reality is that you can treat CIU with non-sedating antihistamines and actually improve people's reported sleep and daytime wakefulness and daytime functioning treating them with a non-sedating antihistamine.

The study that we did at Georgetown was to give people an 8 or 12 milligram dose of chlorpheniramine at bedtime at 10:00 at night and in the morning we gave them a dose of terfenadine. We followed the Harvard Pilgrim Healthcare AM/PM dosing regime.

And we studied their sleep latency the following day all day long from 9:00 a.m. to 5:00 at night. Every two hours they took a nap. With the EG

we could see when sleep latency began. We got the average for sleep latency for the whole next day after a night time dose of 8 or 12 milligrams chlorpheniramine. What we found was that patients getting placebo had a greater than 10 minute MSLT, which is normal.

Those receiving the chlorpheniramine at bedtime and terfenadine in the morning had a sleep latency diminished down to six minutes which is about where a sleep apnea patient would be. It's not inconsequential.

What is also disturbing from that particular study was the patients receiving the 8 milligram dose of chlorpheniramine did not report feeling any more sleepy than the patients on placebo. Yet they were clearly physiologically impaired in their ability to stay awake.

You can also look at a study we recently submitted to the FDA, a contract research study that we did at Georgetown, showing impairment seven hours after dosing even with doses as low as two or four milligrams chlorpheniramine. Seven hours post-dosing

is impairment on tracking testing.

Summarizing, successful treatment of CIU does not depend upon sedating the patient. Sedation in CIU is an adverse event and one that can be avoided. Non-sedating antihistamines are as effective as sedating antihistamines in treatment of CIU.

Patients who have been previously diagnosed with CIU, as I think we saw this morning, maybe they're not good at self-diagnosis but the issue of recognition. Can they recognize the disease? I think that was demonstrated. Obviously I think these patients would benefit from access to a non-sedating over-the-counter antihistamines.

Finally, the impact and risks of sedation can be reduced by making a non-sedating antihistamine available over the counter. Thank you very much.

DR. CANTILENA: Thank you, Dr. Kay. Our next speaker is Dr. Engle, Dr. Janet Engle.

DR. ENGLE: Good afternoon. Thank you for the opportunity to present the views of the American Pharmaceutical Association, a national professional society of pharmacists.

I am Jan Engle. I'm Associate Dean for Academic Affairs and Clinical Professor of Pharmacy Practice at the University of Illinois in Chicago. I'm also President of APHA.

My comments focus on the role of the pharmacist in helping consumers navigate the use of loratadine in the OTC environment. Particularly if they may need to seek care for chronic conditions such as chronic idiopathic urticaria.

APHA's 50,000 members include pharmacist practitioners, pharmaceutical scientists, and student pharmacists. APHA members provide care in all practice settings such as community pharmacies, hospitals, long-term care facilities, managed care organizations, hospice settings, and the military.

In each of these settings pharmacists help consumers manage and improve their medication use including the appropriate selection and monitoring of prescription and over-the-counter products. Ensuring the public's health and safety, especially with respect to medication use, is the pharmacist's and APHA's highest priority.

In the interest of full disclosure, APHA frequently partners with federal agencies, consumer groups, and the pharmaceutical industry and others to help develop educational programs. The association did not receive funding to participate in today's meeting and the views that I'm presenting are solely those of the association and its membership.

The pharmacist's role in OTC drug use is different from the role that is provided by other healthcare providers. Most OTC products are purchased at a pharmacy positioning pharmacists to work with consumers at the point of decision making and purchase.

Pharmacists serve as the bridge between consumer self-care activities and interaction with the formal healthcare system. Today I will address the pharmacist's role in bridging these two systems in the context of loratadine and its use for CIU.

APHA agrees that the proposed switch of loratadine from prescription to nonprescription status may potentially improve patient safety and clinical outcomes by expanding consumer access to therapy with

fewer sedating side effects than with the available OTC products.

Important to the safety equation, however, is the appropriate use of the TOC product and this is where pharmacists can help. Pharmacists can and do play and valuable role in helping consumers use OTC products for short-term treatment or symptom control in acute and chronic situations and recommend physician or other prescriber involvement when acute or chronic conditions requiring additional attention are identified.

Pharmacists work with consumers and prescribers every day to selected appropriate medications. The proposed switch of loratadine to OTC status for the treatment of allergic rhinitis and diagnosed chronic idiopathic urticaria can be successful.

Proper symptom identification by consumers and pharmacists will be essential to appropriate use. Each day pharmacists assist in the proper identification of nonprescription medicines to treat a number of clearly identified and easily treatable

conditions.

OTC products have been used to treat allergic rhinitis for many years. Expanding access to non-sedating antihistamines will improve OTC management of this condition. Currently we have no OTC options to treat CIU. Approving loratadine for the OTC treatment of previously diagnosed CIU after analysis of appropriate studies of safety and efficacy and labeling comprehension will improve management of this condition.

Pharmacists can help assure that consumers using the product to treat CIU have had this condition diagnosed by a physician, are not experiencing an acute anaphylactic reaction, and are using this product appropriately. I think those are some of the issues that came up this morning.

The success of the pharmacists efforts in this role, however, will be directly related to the amount of information available to them. Product labeling should clearly articulate the situations where self care or OTC use is appropriate and direct consumers to their pharmacist or their physician when

the use of the product falls outside of label parameters.

Additionally, an extensive educational campaign geared toward pharmacists to equip them with the proper tools to identify triage and select OTC treatment for CIU will be needed. Pharmacists are in an excellent position to work both with physicians and consumers as well as the industry and government agencies to improve patient outcomes associated with nonprescription medicines.

Whether it be by patient compliance strategies, medication assessment, counseling on proper usage and side effects, and identification of patients who need therapy, pharmacists are committed to engaging in activities to promote better healthcare for all consumers.

My comments today are supported by the action taken by our APHA's House of Delegates which is our policy making body for our association. In March of 2001 the delegates debated and adopted policy on this issue. Our adopted policy reads, "The American Pharmaceutical Association as an issue of public

safety encourages manufacturers and the food and drug administration to transition non-sedating antihistamines from prescription to nonprescription status."

The nation's pharmacists encourage the FDA and manufacturers of second generation antihistamines to embark on a reasoned path to increase access to these products. Thank you for your consideration of the views of the nation's pharmacists.

DR. CANTILENA: Thank you, Dr. Engle. Our third and final speaker in the public comment section will be Dr. Joseph Ferguson.

DR. FERGUSON: Distinguished members of the FDA, distinguished representatives of Schering, ladies and gentlemen, including the man in the back who has been snoring all day, I am very appreciative of this opportunity to speak before you. It is truly an honor for me.

In the interest of disclosure, I have worked as a consultant for Schering as well as Pfizer, the makers of Zyrtec, and I am currently doing clinical research for Adventis, the makers of Allegra.

I'm here today after a Schering representative suggested that I speak at this meeting. Neither Schering nor any other corporation nor individual has offered compensation for my appearance today. No one has stated or implied that I will be rewarded in any way. My expenses for attendance at this meeting will not be reimbursed.

I'll be speaking today for only a few minutes and I'll limit my comments to the question of whether loratadine should be allowed to have over-the-counter chronic idiopathic urticaria indication. I will leave to others the question of whether to broaden the indication.

The title of the talk is, "To deny loratadine, the over-the-counter indication for chronic idiopathic urticaria, is to misinform the American people." It's my opinion that a prescription antihistamine that has been proven to be effective in treating chronic idiopathic urticaria should not have that indication striped simply because the drug has been found to be appropriate for over-the-counter use.

Instead, the antihistamines should have a

label that might read as follows, "This medication can be useful in the treatment of chronic idiopathic urticaria (unexplained hives that keep coming back). Anyone considering the use of this product for urticaria (hives) should first seek prompt medical attention."

I'll repeat that. "This medication can be useful in the treatment of chronic idiopathic urticaria (unexplained hives that keep coming back). Anyone considering the use of this product for urticaria (hives) should first seek prompt medical attention."

Such a label would be an education for the American public. A man who has been using antihistamines for what he thinks are recurrent hives would realize that maybe it's time for him to check in with his primary care doctor before he continues to self-treat.

So what if the man does not want to see his physician? If a person who should be getting medical attention makes an informed decision not to do so, it is not the place of our government to step in

and force medical attention on that person obviously.

Nor is it the place of our government to withhold information from the public such as the fact that a certain antihistamine was found to be safe and effective in the treatment of chronic idiopathic urticaria.

It is not the place of our government to withhold information from the public just because there are people who would make informed but unwise decisions with that information.

Nor is it the place of our government to seek out those who are eating too many cheeseburgers and send in nannies to make them eat broccoli. It just doesn't make sense.

I would appreciate it now if you would allow me to finish this talk by indulging in a bit of speculation, speculation about an America in which loratadine has been approved for over-the-counter use, but the makers of loratadine have been forced to keep quiet about the fact that the drug has been found to be safe and effective in the treatment of chronic idiopathic urticaria.

A woman, a long-distance truck driver, has chronic idiopathic urticaria. She has seen her physician who has ruled out the dangerous causes and a prescription antihistamines has been quite effective in controlling her symptoms over the years.

But here she is now. She's 2,000 miles away from home and she is struck with the most ferocious case of hives she's ever experienced and she realizes that she forgot to bring her prescription antihistamines. She is itching like crazy. It's even dangerous for her to be driving but she manages to make it to a truck stop.

She runs inside and she finds the isle with the allergy pills. She picks up a body of loratadine which is the only one that doesn't put her to sleep, and she is crestfallen when she realizes that that bottle says that this medication is only for runny nose type symptoms, not hives.

Clawing at her skin she slumps back to the truck and figures she'll drive and get in touch with her doctor in the morning. She shutters. It's going to be a long night.

Distinguished members of the FDA, representatives of Schering, ladies and gentlemen, thank you so much for your time and attention.

DR. CANTILENA: Thank you, Dr. Ferguson.

Before we get to the open committee discussion, what I would like to do is offer the members of the committee an opportunity to get an unanswered questions, anything that they would like to ask of the sponsor or of the FDA presenters, anything that was not completely covered in their minds this morning that they would like to first obtain information before we get into the open discussion. Does anyone have any questions?

DR. DYKEWICZ: I would like to follow up a bit on some of the data that was discussed earlier about the actual usage of medications when there has been a stipulation or a statement within the product labeling for the patient not to use it. I believe the example that was given was for the antifungal products to be used for vaginal infections.

It really gets at the whole question about actual usage versus what is being placed upon the

product labeling. We know apparently in that particular over-the-counter usage that many patients are using the medication, if you will, inappropriately despite the statements.

Now, in terms of label comprehension, is the FDA aware of any studies that show that people or women were appropriately understanding what the label said but despite that went forward and used it inappropriately anyway?

DR. KATZ: Back when these products first went over the counter, there actually were no label comprehension or actual use studies for the vaginal antifungal products. There have subsequently been some literature that has been published suggesting that, in fact, there are a group of women who may be using the product inappropriately. Not all women who are using the product have previously seen a physician and have had a previously diagnosis.

We don't really have the data that would correlate how well they understood what was in the label and if the reason why they are using the product is that they didn't understand the labeled

instructions, or that they had just chose to use the product because they thought that they really had a vaginal yeast infection even though they have never actually been diagnosed as having one.

DR. CANTILENA: Okay. Dr. Alfano next and then I saw another hand.

DR. ALFANO: Yes. The sponsor presented some data and Dr. Ganley referred to it that 62 percent of people with CIU self-medicated prior to a physician diagnosis.

My question either to the sponsor or to the agency is do we know what percent of people with acute hives premedicate seeking medical attention?

DR. CANTILENA: Dr. Clayton, would you like to try that one?

DR. CLAYTON: We do not have that specific information, but since these individuals use an OTC antihistamine prior to diagnosis, we will assume that episode was an acute episode but it was prior to a physician diagnosis of CIU.

DR. CANTILENA: Dr. Ganley, is there any other information that you have other applications or

products? Okay.

Dr. Joad.

DR. JOAD: I was curious for the FDA about how they felt in general about the general concept of having a drug OTC that prior to that they had to see a physician one time for a diagnosis and then thereafter everything should be OTC.

That strikes me as something I wouldn't like very much because I would like to see a patient back so I could have another shot at that diagnosis if I was wrong. Is that something you plan to do in general or are you comfortable with it and is it a direction for the FDA?

DR. GANLEY: Actually, that's what we were hoping you would answer for us today. I think, though, if you really -- you know, that's why it's pivotal to try to think of this spectrum of patients that are going to take it and try to figure out what's the down side of that.

I think it would be every difficult based on just the facts that we know in this case to ever create any label that unequivocally is going to ensure

that people only with CIU are going to use this product. I think it's virtually impossible to do that.

That's why it becomes important to understand what is the frequency and significance of these other conditions such as angioedema that may be associated with urticaria or acute urticaria. Is that acute urticaria somehow different than this population of chronic in terms of the frequency and severity of conditions.

I think it would be difficult based on the facts we have that people already use it and there's a perception out there that you can use it for these conditions to just believe that we are going to limit it by putting something on a label.

In the converse then if you go down a path that says this could be just for the treatment of hive and then you actually put in labeling or something that defines the parameters of when someone needs to see a physician, repeated episodes and daily for seven days. I think we are having the cart lead the horse here where you're saying that it's only this

population that has a diagnosis of chronic urticaria.

Actually if you put on a label that it's for recurring episodes of hives and people just ignore that they should see a doctor for that actually to get a diagnosis of exclusion, then you may have people that actually use it thinking this is for recurring hives.

DR. CANTILENA: Dr. Temple.

DR. TEMPLE: In some sense this is an issue that arises every time you make an OTC switch whether it's heartburn that may or may not have been bad esophageal disease or the use of low-dose hydrocortisone preparation. Prior to their availability over the counter, there was always a doctor intervening and deciding whether this was serious enough to require recurrent visits.

Every time we do that, that is why we have public discussion of whether it seems like the same thing. The vaginal anti-candidiasis drugs was a very difficult one for us. As you may remember, we turned it down several times before we finally concluded it was okay. This is not unfamiliar territory. That's

why we need advice.

DR. JOAD: Just as a follow-up, it seems to me different between saying somebody can diagnose themselves and, therefore, they go get the OTC versus it's complicated enough that a physician has to diagnose it but then now it's OTC. Those seem like very different things to me.

DR. TEMPLE: You mean the explicit requirement that it be diagnosed first?

DR. JOAD: Right.

DR. TEMPLE: That's why the vaginal candidiasis was just a problem because that's what the labeling said and obviously people knew that not everybody would go to the doctor first for that.

There had been a view that dermatosis that might be steroid sensitive ought to be considered the same way, that you ought to go to the doctor and find out what to do first. We have survived switching them, at least for low-dose drugs, to let patients give themselves a crack at it. But that's why it's hard.

DR. CANTILENA: Yes, Dr. Clapp.

DR. CLAPP: I have two questions. First, could someone from the FDA addressed the data from the UK and Canada. As I recall, since 1990 Canada has had hives as an OTC indication for use. They mentioned that there were no adverse effects noted in Canadian literature. Could you address that more precisely in the UK? That's the first question.

DR. GANLEY: The data I think you may be referring to, and you can correct me if I'm wrong, is the data that Dr. Lee had talked about, and that was information that had actually been reported. We focused mainly on serious adverse events.

As he had said, there were some cases of anaphylaxis and things like that. I think one of the difficulties, and it's a problem in this country as well as in Canada and the UK, is the reporting of these events. You have to have -- there has to be some type of faith in that things are going to get reported that may be a problem.

I think there are some cases that Dr. Lee had talked about which is of some concern, if people would actually have food allergies and think that

mistakenly that you could prevent the allergy by just taking the medicine and you may end up with numerous cases like the woman who ate the seafood pizza. She took it after the fact.

Here, though, if you have a drug on the market where they are advocating use for allergy or urticaria, is this going to create a problem and how do you -- it's really coming down to if it is a problem, how can you prevent that problem whether it's through labeling or education or whatever.

DR. CLAPP: What I was interested in the Canadian experience.

DR. GANLEY: As I said, there are cases of anaphylaxis that have been associated with the use of the drug for the treatment of urticaria. Unless you have more specific, clearly that is one of the issues here is what are the significant adverse events. We would be less concerned with very minor adverse events if someone reports a headache or anything like that.

DR. CLAPP: I certainly understand that. What I was wondering is in the body of research that you have gleaned from, UK and Canada, whether or not

there have been a significant number of adverse events, serious adverse events reported because of the longevity of their experience having used it as an over-the-counter drug for hives. I don't think they mentioned recurring hives but included hives as well as seasonal allergic rhinitis as an indication.

DR. KATZ: I think the question that you're asking, we can only give you some sketchy information because we don't keep track of other countries' adverse event data. We do have one table that was provided to us but the total end that they provide for the adverse events is an end of 26 so we're talking a low number.

Now, I can't tell you over what period of time it is because it doesn't state in the information that's here. But if you look at it, actually it looks like there may be a response from Schering. The adverse events that are being reported here would be things along the line of pain, dyspepsia, headache, urticaria aggravated abdominal pain, back pain.

All of these are numbers that are less than three or three and below. Again, it doesn't

really help you because I can't put it into a perspective of what time frame we're talking about. If this is coming from their adverse event reporting like our Medwatch system, you don't have a denominator.

The numbers are low and the reporting system is whatever gets reported back. There doesn't look like from this that we have that there is anything that would be unusual or unexpected as compared to our own database where the product is Rx.

DR. CLAPP: Thanks. I would like Dr. Chowdhury to address some data he mentioned. In the literature we received it said 79 percent of those who read the labels incorrectly mentioned or identified the use of the drug for just hives, not the CIU indication that is being promoted by the drug company.

In that the interest is inadequate directions for use, how does the FDA feel comfortable representing this drug without addressing the fact that most of those who use it will likely use it incorrectly? Should we address the fact in the direct way that the likelihood is that most of those who use

it will use it incorrectly and then guide them in appropriate usage of the drug?

DR. CANTILENA: I think that was to Dr. Chowdhury. Is that correct?

DR. CHOWDHURY: Is it directed to me? I was not really present on the use study.

DR. CLAPP: You did mention that the likelihood was that it was going to be used inappropriately in your presentation.

DR. CHOWDHURY: Correct. That was a statement that I made, that if the drug is going to be made over the counter for chronic idiopathic urticaria, as we have been talking about this indication, the drug possibly is going to be used for all kinds of urticaria.

DR. CLAPP: With that likelihood, as you mentioned, you said the likelihood was that it would be used for broader indications or other indications for acute urticaria. I think the next gentleman mentioned the label study quoting 79 percent of those who read the label as identifying its use incorrectly as for acute hives or any type of hives.

How do you reconcile giving the public appropriate guidance in the usage if we are pretty clear on the fact that it won't be used correctly by the majority of those who purchase the drug?

DR. CANTILENA: Sure. Dr. Wood will comment on that and then we'll go to the sponsor. I think they have a comment.

DR. WOOD: I think we have to be careful about saying it's being used incorrectly. I think we need to define that. That was sort of the interaction that Lloyd and I had before lunch.

DR. CLAPP: Not for the indication as the CIU indicates.

DR. WOOD: Well, hang on. The CIU, they are going for a limited indication. That doesn't mean that the other indications will be incorrect, No. 1. No. 2, incorrect implies a sort of value judgement that if you were to give it for these other indications, something bad would happen to you.

That was what I tried to put light on this morning. I guess the response I got was that nothing bad does happen to you if you use it for these other

indications. The acute urticaria may not be an appropriate indication.

It's just that it is impossible. As I understood the responses, it's just that it's impossible to study. At least to me, we're not exposing people to increased risk because of that which seems to me the absolute clear bottom line.

DR. CLAPP: I agree but my question is are we guiding them on how to use if appropriately? Are we giving them some indication and guidance for the use other than CIU and recognizing clearly that most of it will be used for the non-CIU indication. Is that a responsibility to then appropriately direct them for the usage in other than the CIU indication? That's my question.

DR. CANTILENA: Right. I think that's a key point. Dr. Temple and then Dr. Clayton from the sponsor.

DR. TEMPLE: Dr. Ganley wasn't trying to push anybody around but if you read his review, he's clearly interested in a labeling that goes toward a more general statement about urticaria than about the

CIU. Part of the reasoning, I think, is just that. A lot of the use is going to be for people who don't meet that test.

If labeling is directed toward that, you are better able to give the best advice you can. Charlie may want to say more about that but that is really one of the questions here. Do you pick out something that happens already to be in the Rx labeling so it's nice and solid and you don't have to worry about where the evidence is even if you know people will use it outside that which, as Alastair said, is not necessarily the wrong thing to do.

It's just not the labelled thing to do. Or do you try to write a broader indication and do you have the data that allows you to do it and then give advice that corresponds to how it is actually going to be used. I think if you read his review, he raises that very question also.

DR. CANTILENA: Yes, Dr. Clayton.

DR. CLAYTON: There's a number of questions on the table since I stood up. I really stood to try to clarify the Canadian experience if

that was still needed. I think Dr. Katz helped to put that in perspective. The database was with the 10 years of marketing experience since the product was launched in Canada so it is over quite an excessive time period.

The adverse event experience tracks very clearly the experience with allergic rhinitis overall with types of adverse events, both the prescription experience and the OTC experience, CIU, and allergic rhinitis. We can address specifically the numbers if there is still confusion if that would help.

I think there is also a question about the survey in terms of the respondents who answered incorrectly. The 79 percent number was of the 30 percent, the 79 percent of the 30 percent who answered incorrectly. If there is any confusion there, hopefully that can help to explain it.

Is there any value in pursuing the Canadian? We could get into the specifics if that is still an issue.

DR. CANTILENA: No. I think that is probably okay of that's all right with you, Dr. Clapp.

Dr. King.

DR. KING: I'm just reminded that all these kind of things they've gone through often times you say you have to see your doctor first so it's like justice delayed is justice denied. Denying people access to these medications brings up the issue of education and accessibility.

Dr. Engle's presentation that pharmacists are in a primary position to be available 24/7 and then to advise folks there, there is a counterweight to that. People either go to the emergency room or they go to the pharmacist in general. They may stop at truck stops. I'm not in that crowd.

Anyway, it seems to me the issue is if we are going to talk about why would the FDA considering broadening the indications, we have to talk about what are the real indications and what is the real affect.

It seems to me if you have available a system of pharmacists, the change of labeling and just basically a good old fashioned spin of TV and web kinds of things where you educate the public, I think everybody has a right to do something dumb and stupid.

Just because 40 million people do something dumb and stupid, it's still dumb and stupid.

I'm not going to get into that issue. I think the issue is education and accessibility. I think there is everything on the table to think about maybe broadening it through access and to general limitations on this application are not going to work.

I think people are going to take what they want to take and have a system of pharmacist and education and labeling actually could improve the overall use of this drug and prevent lots of people not doing something dumb and stupid.

They will know in multiple directions from the label, from the pharmacist, and their back door neighbors. They are likely to get much better care than they are right now.

DR. CANTILENA: Yes. Dr. Ganley, do you have any idea in terms of the amount or the percent of over-the-counter drugs that are actually sold outside of a pharmacy like in the truck stop or the gas station?

DR. GANLEY: No, we don't have any

information like that.

DR. UDEN: Dr. Engle's talk had a reference in there that 61 percent of prescriptions are purchased in a pharmacy.

DR. CANTILENA: Thank you, Dr. Uden.

DR. UDEN: Not of prescriptions. All of prescriptions are purchased in a pharmacy. You mean OTC meds.

DR. CANTILENA: Yes.

DR. SZEFLER: I'm going to ask a simple question, and maybe I missed it in the reading, but if loratadine was not going up for OTC and if they presented these two studies for chronic idiopathic urticaria, would that be sufficient to approve labeling for prescription use?

DR. CHOWDHURY: Yes.

DR. SZEFLER: For that indication.

DR. CHOWDHURY: For chronic idiopathic urticaria. Those studies were the basis for approval for chronic idiopathic urticaria.

DR. SZEFLER: Okay. So you don't have any trouble in terms of its indication for that?

DR. CHOWDHURY: That's correct. For indication only.

DR. WOOD: It's already approved for that. That needs to be clarified.

DR. CHOWDHURY: I mean, that was a question.

DR. WOOD: Right.

DR. CHOWDHURY: Were the two studies adequate for approval for chronic idiopathic urticaria and the answer is yes, there are two.

DR. CANTILENA: And how about in terms of the indication of just hives in general? Do you have efficacy data that would support that indication?

DR. CHOWDHURY: Well, I mean, currently Claritin is not approved for anything beyond symptom control of chronic idiopathic urticaria. That really has not been an application. In other ways would those studies be adequate just to give their approval in a prescription setting for urticaria of other kinds? The answer possibly is going to be no without really probably going into the full rationale for that and --

(Whereupon, off the record.)

DR. CHOWDHURY: -- which perhaps can be done for other types of urticaria.

DR. CANTILENA: So the purpose of -- I mean, sort of question 1A then, you don't have efficacy data that would support an indication of hives then?

DR. CHOWDHURY: That is a question, I think, for the committee to discuss, but there is no data outside the chronic idiopathic urticaria.

DR. CANTILENA: Thank you.

Dr. Wood.

DR. WOOD: I think we are sort of getting hoisted by a patod that goes something like this, that when drugs are approved for prescription indications, they are approved on the basis of the studies that were done with sometimes incredibly complex. If you think of some of the heart failure indications, some of the indications there were incredibly complex based on the studies that were performed.

Once you try to translate that into an over-the-counter indication, it seems to be we need to

be less rigid. There is little point just because CIU was the prescription indication insisting on that wording in an over-the-counter label. It seems to me counterproductive and doesn't serve patients well.

I think we need to step back from a rigid position that says this is what the study said, this is what the definition was in the paper that was published, and move towards the sort of, if you like, the Tennessee view that preferred earlier on.

We need to translate it into words that mean something to patients. I don't think CIU, which is now being tossed around here as though we use that term everyday, is really going to be helpful to the majority of patients who walk into Dr. Engle's Walgreens or whatever.

DR. CANTILENA: Dr. Temple.

DR. TEMPLE: Based on conversations among the people at FDA at least who are supposed to know about these things, it seems quite uncertain as to whether we would think new data would be needed for a claim of simple hives or not.

Mechanistically there's a belief that

we're talking about the same thing. I don't want to dismiss the concern, although I think Alistair is right. Maybe you owe some practical look. I don't think there has been an internal decision that we don't have that data or do and it's something we need to think about. I'm sure advice would be welcome.

DR. WOOD: Bob, the issue I think is not the one that you're dwelling on. For the average person they would translate -- they would see urticaria and hives as being words of equivalent meaning, hives being a word that is much more in widespread use than urticaria in the population that is going to buy drugs over the counter.

I don't think we should force ourselves into a box that says the only vocabulary that can be used for the label is the vocabulary that was used in New England Journal that got the drug approved for Rx indication.

That's different from the -- that's one issue. Then the acute hives is an additional argument that can be entered into. Just translating urticaria into hives doesn't seem to me to need a study.

DR. TEMPLE: No. That's perfectly right. If people eventually concluded that CIU was a really distinct disease from one episode in response to something, then you would have to ask do those data apply. That seems like a legitimate question, but I don't believe there's an agreed on answer internally yet. It does appear that there haven't been any, or very few at best, actual studies of acute episodes of hives.

DR. WOOD: But you would be comfortable with chronic idiopathic hives?

DR. TEMPLE: Oh, I don't think anybody mines that.

DR. WOOD: As idiopathic would mean very little to most people, you would be prepared to drop idiopathic?

DR. TEMPLE: No. Whether you translate the language that you do think you have -- sorry, the disease that you do think you have data for into a different language is the sort of thing you have to think about all the time.

There's always worry about whether people

understand your indications. There is a separate question of whether there is a different disease here. I certainly have no opinion but there was a divided view when we were talking about it, or an unsettled view anyway.

DR. CANTILENA: Okay. Dr. D'Agostino and then Dr. Wilkin.

DR. D'AGOSTINO: Yeah. Well, some of my comments have just been aired there. I don't see any problem with having hives being used for this condition when we're talking about long-term and so forth. My difficulty comes with the acute. If hives is being used in just a generic sense, it encompasses the acute also and what do we have on that.

When I started with the FDA back in the '70s they used to have this grasp, "Generally recognized as safe and effective." I hear a lot of that going on here that somehow or the other the field is comfortable with the use of the drug. I don't know enough about the process and what have you to object to that.

I think that in many ways once we move to

hives, to me that's our real issue, do we have enough sense that the acute is going to be included. If we don't, then I think we are going to get ourselves in a real bind with how to handle that with new studies and what have you.

DR. CANTILENA: Dr. Wilkin.

DR. WILKIN: Yeah. I actually have a concern that some patients who have CIU suffer from a nomilism kind of issue that if they are told they have chronic idiopathic urticaria, they think they have something that is fairly specific. What they really have, as you have translated it, the urticarial hives. Idiopathic means they had a workup but nothing was found. Chronic means it's been there longer than six weeks.

Maybe it's because I trained in Tennessee but I've always had the notion that you call it chronic idiopathic urticaria perhaps because you can charge more than if you say you have hives, you've had it longer than six weeks, and I don't know what it is.

There's a point to this. It could be many different kinds of things still. Calling it CIU is

not a thing. It is the residue after you've taken the things that you know out.

DR. WOOD: Right.

DR. D'AGOSTINO: Are you answering my question? Are you saying that acute hives is really just the same and it's all vocabulary?

DR. WOOD: No. That's a different question. There are two questions on the table. One is, is acute hives the same as chronic hives in terms of response. I think the answer to that is we don't know. At least that is the answer I'm hearing.

The second question is does telling a patient that they have chronic idiopathic urticaria, which translated into the vernacular means chronic, it's been there for a while, idiopathic meaning the physician doesn't know what's causing it, and urticaria being hives, if you translate that into you've got chronic hives and forget that the physician doesn't know what caused it, I don't see that adds much or loses much frankly.

DR. D'AGOSTINO: I think that's great. I think it's the acute hives that --

DR. WOOD: We can show results on the issues if we take some of them and deal with them, I think.

DR. CANTILENA: Yes, Dr. Rosenberg.

DR. ROSENBERG: If I may, I'll try and answer what I think is a good question. Is acute urticaria one thing and chronic idiopathic urticaria another thing, or is it just that chronic is the same thing but we still haven't figured it out?

In preparation for this meeting, I tried to do some reading and I must say I was very taken with this supplement to the Journal of Investigative Dermatology which is our premier research journal.

It's the official journal of both the European Society for Investigative Dermatology and the American one. This was released in November 2001. It's the account of a proceeding held in Europe the preceding year, I must say, under the auspices of the -- in Berlin in the year 2000.

Somewhere it mentions that the UDC company sponsored this meeting. It has really all the very good people from Europe, or many of the very good

people from Europe there. I know these names and I know some of these people.

They say that acute urticaria you usually know the cause. Maybe not the first time but the second time. It hits very quickly and the sufferer can get an idea what's happened, or somebody makes sense of it very quickly.

Apparently the feeling here, and they are quoting work from Switzerland and Berlin, it's a bonafide allergy and there's an instant reaction. It's on and off. The juxtaposition in time makes it.

The word that was unfamiliar to me turns up in here called pseudo-allergy. Most of the other material -- I can show some of this stuff in a little bit. Most of the other that accounted for what we are calling chronic idiopathic urticaria is not that kind of an immediate reaction. It does not show up on the allergy skin test.

In fact, what it is it's all the other material that was on Jonathan's slide that he showed where all the other parts of the immune system come into play and act on the final cells including the

mass cells rather than just the particular allergen.

That's an explanation for why analgesics -- it's not just aspirin. It's things that look and work like aspirin all seem to do it. They divert the immune response system somehow. There's work in here that if it's really a food to which you are allergic, or a product which you are allergic, you are better in a few days when you stop it.

But if you're dealing with what they are calling pseudo-allergy, you have to be off the food or whatever and certain natural foods. Tomatoes are mentioned and others that have these properties in some people. You have to be off of it for some months. There's one claim in here that patients who do this conscientiously that 60 percent get better which is much better than anything we are doing over here.

Again, I'll keep reverting to the enormous use of prednisone in the practice of medicine in all the different specialties for this condition. It's inappropriate in my opinion. Thank you.

DR. CANTILENA: Is there a comment from

Dr. Monroe, the sponsor?

DR. MONROE: I would just like to say that I'm not from Tennessee but I'm going to try and make this as simple as I can. I view urticaria as a spectrum of a disease and it can be classified as acute or chronic and that is a totally arbitrary time limit.

As Dr. Wilkins pointed out, the basic pathophysiology of all urticaria is that slide he showed with the mass cell at the center, the release of the mediators, multiple mediators, but the best documented mediator is histamine and that's the same in acute urticaria, that's the same in chronic urticaria, that's the same in chronic idiopathic urticaria.

I think if you're looking at what's going on, there's a common theme. Are there differences? I think you alluded to some excellent differences. If any chronic idiopathic urticaria is a more complex pathophysiology where you've got a cellular and inflammatory response on top of the more simplistic acute urticarial response. That's what makes that

subset any harder to treat.

I think the message that I would carry away is histamine is the mediator involved in the whole spectrum. We have different causes on the acute side. They are usually identifiable causes but what we're treating is the symptom that is being generated by the release of the histamine.

We're not curing the problem. The reason acute urticaria is an easier problem is we can usually identify the cause and move it out. The drug therapy is totally symptomatic to affect what has already been released whether it's acute or chronic.

To me the issue of are antihistamines, H1 antihistamines, going to be effective in acute. The answer is they are the standard of care approved in all algorithms published by the leading specialties in allergy and dermatology where urticaria is in their domain heavily. I think clearly that is the way to treat.

It is very difficult, however, to do a scientifically controlled study in acute urticaria because it's a very self-limited short disease.

Again, if you look at the basic underlying chemical that is causing the problem, it's histamine.

If you look at the accepted standards of care it's H1 antihistamines. If you look at the real world, most of those patients are self-treating, never seen a doctor, and using much less safe medicines with side effects right now. I think we have clear scientific evidence that urticaria as a whole has the same basic mediator and the same first line treatment.

DR. CANTILENA: Okay. Thank you. Dr. Davidoff.

DR. DAVIDOFF: This has been a very interesting somewhat academically oriented discussion and through a rather sort of tunnel vision, it seems to me, in terms of the broader problem. I think that the average person coming into the drug store with a skin problem that's bothering them because it's itchy and maybe somewhat red isn't going to be trying to make this fine distinction between is it acute hives or is it chronic hives.

I suspect that -- well, I guess my question really is are there data on how the general

public decides to call something hives? My suspicion is that they frequently refer to something as hives that a dermatologist or an internist or family practitioner would not call hives. Even if you use hives as the word on the package, my question is how frequently will that be helpful in guiding people?

The flip side of that question is since a great fraction of all skin conditions itch, are there data on how frequently that itch is relieved in things other than hives by antihistamines? If they are frequently relieved, then that's going to be positive reinforcement they will continue taking it and then not be seeing the dermatologist or whoever to try to get a proper diagnosis made.

I wonder if there are data in those two areas? How do people define something as hives and how often is that correct? Secondly, how often do non-hives and itchy skin conditions respond to antihistamines?

DR. ROSENBERG: If I could answer that. The antihistamines are really not very good for itch per se. They are not very effective atopic

dermatitis. They work more as sedatives, the more sedating the better. They are really not -- atopic dermatitis doesn't go this way or it's got a little piece to it. Eczema Dr. King says for those.

This really is a histamine induced disease, as Dr. Monroe has said. The antihistamines really shine here. This is where they have a place in treatment of itch.

DR. CANTILENA: Yes, Dr. Lam.

DR. LAM: I still have a concern that consumer is placed a tremendous burden in terms of knowing not to use the product without seeing a physician. Usage data from fungal vaginitis would suggest that's not the case.

My question to sponsor is given this fact of all the educational program that they have proposed in slide No. 78 in the presentation, in their experience which one actually is most successful in terms of reducing this type of misuse behavior? If none of them is reasonable or successful, do they have any innovative program on the drawing board?

DR. CANTILENA: Dr. Clayton, would you

like to address that for Dr. Lam?

DR. LAM: Do you want me to repeat the question?

DR. CLAYTON: Yes, please.

DR. LAM: Of all the educational program that they have proposed in slide No. 78 in the presentation, in their experience which one actually is most successful in terms of reducing this type of misuse behavior meaning that they should actually not use it without seeing a physician and if none of them is appropriate or successful, do they have any innovative program on the drawing board?

DR. CLAYTON: We have used this approach with prescription drugs. We have not used it to this point with OTC drugs. We'll be building off of that experience. I don't think that there have -- I'm not aware of any test data that point out which path is the most successful but rather a combination of approaches to achieve the end result. Education is clearly key.

There has been a lot of discussion about experience with vaginal yeast products and has been a

success, I believe, on migraine which uses the very same approach. I think it is important to point out that the experience now 11 years OTC with vaginal yeast products has been a very positive one in terms of the safety experience.

There are certainly cases we acknowledge of failure to achieve a physician diagnosis in advance. There are studies out there also that support that the incidence of inappropriate use is low.

There are also studies that show people self-treat with home remedies at a fairly high percentage that tend to do harm. I think it's a combination of various approaches to education to really work toward solving the problem.

DR. CANTILENA: Yes, Dr. Sachs.

DR. SACHS: Anyway, it seems like we are kind of circulating around the main issue which would be that if we agree that an OTC indication for CIU would be given that were basically kind of approving it for a more broader indication of hives, versus the other which would be to just continue it for the

allergic rhinitis indication and educate the affected patients who are seeing their doctors anyway, that would be permissible to take something that's already OTC for their condition which is kind of a backhand look at it, okay?

DR. UDEN: Dr. Sachs, do you believe that if Claritin went OTC for allergic rhinitis that if they went to see their physician, they wouldn't walk out with a prescription for Clarinex instead?

DR. SACHS: Actually, I don't like writing prescriptions so it would be recommended at least in my practice.

DR. CANTILENA: Yes, Dr. King.

DR. KING: I guess if I understand that you're saying that if we left it like that, you're going to encourage the physician to promote the off-label use of a drug? I don't think the FDA would want to be in that position if you understand what I'm saying. Either it's a yes or no.

DR. SACHS: If it was approved over the counter for the indication of allergic rhinitis and it's also approved for chronic idiopathic urticaria,

then would it have two classes, I guess. At a practical level I didn't think it would.

DR. KING: I just have that problem. I think there is one way to get some data here. One of the things I thought about is that the most common cause of workman's compensation claims are for skin problems. The most common workman's compensation disability is for joint and muscle pains.

There's a whole batch of data from the NIOSH and so forth and companies who are in a financial position to keep up with nurses and the workforce and so forth. I think you could get at that database for how many patients had itchy rashes, whether it's urticaria or it's contact allergy or irritants from manufacturing or whatever.

I think the FDA is not in a position necessarily to talk across the government lines, but I think there is a database there we are just ignoring because there's going to be a whole lot of antihistamines and a whole lot of other things given for workman compensation kind of things so I think we could look at that. I just don't want to get in a

position recommending that physicians do with federal sanction off-label use of drugs. That puts everybody at risk.

DR. CANTILENA: Yes, Dr. Johnson and then Dr. D'Agostino.

DR. JOHNSON: I have a couple questions that I would like the dermatologist to answer and then the latter question I would like the sponsor to also address. The first centers around what the actual need is for the physician diagnosis in most of these situations. Is it, in fact, necessary to be diagnosed or will most people if they self-treat for a period of time and don't have resolutions seek medical care anyhow? That's my first question.

DR. KING: I'll start. One of the things that keep allergists and dermatologists in business is itching. People are just not going to ignore itching for a long time. It's just one of Mother Nature's kind of thing from the cave.

If you've got bugs on your skin, you start itching and you're really going to go after it so I think the dermatologists take the viewpoint it's often

times that you're just not ready access and that people are going to self-treat first and then they are going to go to primary care doctors or pharmacists or whatever.

I think the fundamental issue is that I don't think it's a problem from the dermatologist point of view saying you can't charge or you can't whatever. It's a matter of access.

If people have it persistently, then you are going to have to do the workup because there is this five percent that have related to cancers, related to connective tissue disease and so forth. We're at the end of a long tunnel and for my purposes, the land of the rare, the rare is common.

I have a misperception of I don't see nearly as many people with urticaria as the pharmacists do. I have no problem with their education system, their labeling system. When they get to me it's already tests for thyroid, tests for other things so it's a very limited population.

DR. ROSENBERG: If I could take a crack, the question is is it all right if people should treat

themselves without prior diagnosis by a physician. I have something I want to say about that.

First of all, there's the acute severe urticaria that no one is talking about here. When it's very severe, people know that it's severe and they medical attention the only way they can get it which is in an urgent clinic or emergency room or they dial 911.

We know that people in general make the right choices. There are lots and lots of studies that show that self-medicators have more education and do better and have better health outcomes than people who seek medical care on all occasions. The really bad cases that need epinephrine are not part of this system.

Now, there are two more cases. There's acute urticaria that's not life threatening. All of a sudden you've got itchy hives. You've never had it before. Then there's the other case where you've had episodes before and before and before and now you have it again.

Let's talk about the two of them. First,

acute urticaria. It's the first time you've ever had it. It's hard to see a dermatologist without waiting a couple of weeks for an appointment. I don't think I see much acute urticaria except in family members and in house officers and nurses.

To go back to this symposium that I'm so taken with, it's a discussion of urticaria in general. One of the items in here is a consensus statement, "The Management of Urticaria - A Consensus Report" by these professors from prominent people in Europe, Vienna, London, Berlin, and so forth.

First, type of urticaria A, acute urticaria. The standard treatment, non-sedating H1 antihistamine. This standard treatment for acute urticaria is non-sedating H1 antihistamine. That has a little superscript A which says, "Efficacy proven by double blind placebo controlled studies," but I can't find the references here in this paper. I'm sure it will show up otherwise.

An alternative treatment, second choice for acute urticaria is initially prednisolone 50 milligrams a day for three days. You don't see many

three-day prescriptions around our way. That's their second choice if this didn't help.

Next we go to chronic urticaria. The standard therapy, the first therapy for chronic urticaria according to these European professors, non-sedating H1 antihistamines, again with a superscript A, proven in double blind.

The second standard treatment if that doesn't work, increase the dose if necessary. Now there is a list of alternative treatments. They are listed as alternative treatments. I'll read down the list of them because there are 12 or so. I'll go quickly.

Combination dapsone and pentoxiline, combination H1 and H2 blockers, combination H1 blocker and beta sapathomymedic (phonetic), i.e., terabutaline, combination H1 blocker and cykatrophic (phonetic) drug, trisiclic (phonetic) antidepressant doxipen (phonetic), danisol, stanisol (phonetic), lucotriantagonsis (phonetic), selfosalozine (phonetic). Corticosteroids come in after all this other. Cyclosporin A, wow. Interferon, poova

(phonetic), plasmaforesis (phonetic), and immunoglobulants. The corticosteroids coming in about 12.

Again, that data we saw from the company showed that 40 percent of primary care doctors, that's their first treatment, not non-sedating antihistamines, not non-sedating antihistamines at a higher dose but first. And 28 percent of the pediatricians and so forth.

I mean, if you talk in terms of what's the worse thing that could happen if somebody got hold of some of this, aside from the 911 cases, what's the worse thing that could happen? They are right in line with the European standard for both diseases and better than they are going to get in most medical offices in the United States of America.

DR. WOOD: But the worse thing that could happen is they go to the doctor. Isn't that right?

DR. ROSENBERG: If we force them to go to the doctor because they can't get an over-the-counter thing without waiting until a week from next Friday, yeah.

DR. CANTILENA: Did you have a second question, Dr. Johnson?

DR. JOHNSON: My second question probably is more directed at the sponsor. If I recall in the background materials that we were provided, there was an expert panel that was convened and it said that their recommendation was to pursue or that the indication should be limited to CIU.

I guess from what I've been hearing today, is that because that expert panel really perceived that there were risks associated with sort of the broader indication or it just seemed to be the safer easier route to pursue?

DR. CANTILENA: Yes, Dr. Monroe.

DR. MONROE: I was a member of that expert panel. The expert panel simply addressed the issue of taking the prescription indication over the counter and felt very comfortable with that. That would be the CIU indication.

The expert panel did not address the broader indication. Personally as one member, and in my presentation, I don't see any harm in the broader

indication but that panel simply addressed the narrower. They did not have reservations and didn't address that issue.

DR. CANTILENA: Yes, Dr. Sachs and then Dr. Dykewicz.

DR. SACHS: It has been stated to my kind of surprise by both the FDA and by the sponsor that it would be very difficult to do a study in acute urticaria.

As a clinician participating sometimes in research trials in my office, I'm kind of struck by I don't think it would be that hard given that we do studies, for example, on croup which is an acute self-limited disease that last maybe two to three days, that can be either spasmatic and may occur one time in the middle of the night type thing.

It would not be a tough thing to do to do such a study in the ER other than the fact that it might be a little more difficult to do placebo because of the wider acceptance of antihistamines already.

Having said that, I'm not sure I have such a big difficulty in the use of these antihistamines

and hives. I am just wondering more about the broader sense that it's okay for us to say, sure, without efficacy data it's okay to broaden an indication for a drug that would be used so widely over the counter.

DR. CANTILENA: Yes.

DR. WOOD: I don't think I was arguing for broadly an indication. The issue we're discussing is the risk of it being misused in an indication for which it's not approved. That seems to me a fundamentally different argument.

DR. CANTILENA: I think actually question 1A is asking us should it be broader.

DR. SACHS: I think the reason that we're asking that question should it be broader is because it is totally unrealistic to expect that it wouldn't be used for acute hives or other urticarial as demonstrated by the sponsor data, by our experience with use.

DR. CANTILENA: Yes, Dr. Dykewicz and then Dr. D'Agostino.

DR. DYKEWICZ: I would like to direct the question head on as to what the potential adverse

outcomes would be of inappropriate use by the consumer of this medication for urticaria of all sorts of ilk, acute versus chronic idiopathic.

I can see several potential areas where there would be potential adverse outcome. Take, for instance, the example of use for acute urticaria for food. There, on one hand, would be the concern maybe based upon particularly, I think, the specter of what Dr. Lee had presented this morning about some of the patients who are developing anaphylaxis on the antihistamine agent.

I think there would be the consideration that you would have some people who would feel, shall we say, comfortable dealing with food induced urticaria by the availability and the indication over the counter for treatment of urticaria by this product.

They might be kind of lulled into a false sense of security that they can treat this themselves, that they can suppress maybe even a food allergic reaction from occurring, and they may miscalculate with the result being anaphylaxis and death. I

actually think if you're looking at worse case scenario, that is something that is going to happen.

I think one of the things then that would have to be considered is the frequency of that happening and that for the greater benefit of society is that a risk that is balanced by the greater benefit to society. Unfortunately, I think in terms of trying to assess what the frequency of that would be, we are really not going to know.

Another food related issue that comes up, and I do see this when patients come into the office, is the patients have been under the belief that their urticaria is food related so they have been self-treating themselves with currently available over-the-counter antihistamines.

The reality is that they have inappropriately assessed that they are allergic to foods and they are, in fact, getting nutritionally deficient diets as a result. They've eliminated wheat products, dairy products, meat products. You really are seeing a patient who, I think, is having some adverse outcome on that basis.

Then, of course, the other issue is, and this is why the original indication was trying to be restricted to chronic idiopathic urticaria where there has already been a prior physician evaluation, and that would be these less common but real issues of a patient who has maybe some connective tissue disorder or urticaria vasculitis where they may be getting some benefit with their skin condition by the use of the over-the-counter product, but then we less likely to seek the attention of a physician of medical intervention and, thereby, allow the progression of the underlying disease process leading to, among other things, some renal disease.

I think there are certainly a number of situations or scenarios that could occur where the inappropriate use in the broad stroke terms of this agent over the counter for urticaria might lead to some adverse outcomes.

I think the dilemma that we are facing here is that even if you tried with all the product labeling as has been appropriately proposed, even if you tried to warn the consumer about all of these

different concerns, would the consumer heed these in practice or would actual use be such that there would be just kind of across-the-board use of the products with some of the adverse outcomes that I've discussed.

DR. UDEN: But those would not be because they are taking antihistamines. All those examples you cited were because they would have delayed seeking medical care. They would have been driven to take antihistamines for some reason.

It's just like when you go to see a physician, "Oh, no. I've got to do it Friday night at midnight," something happened that they are seeking treatment. It's not really antihistamines that are causing those issues. It's really them delaying going to therapy.

DR. DYKEWICZ: Right. It's not an adverse effect of the medication. It's that, say we say, the certain amount of comfort level that they may have that they are doing the appropriate thing with the over-the-counter product might thereby decrease their threshold or change the threshold for seeking appropriate medical intervention.

DR. UDEN: I hear that but I don't hear in your examples like when we discussed phenylpropanolamine here and people were dying of -- had a risk of hemorrhagic strokes or dying, I'm not hearing that level of concern of medical catastrophes by delaying a diagnosis.

DR. CANTILENA: Okay. Dr. D'Agostino, Dr. Temple, then Dr. Alfano.

DR. D'AGOSTINO: This is for Dr. Wilkin actually. I'm trying to figure out one can take the data that we have and say that we can bring it down to acute high situation and feel comfortable with it. Now, if you go into other fields like analgesics, periodontal fields, and weight reduction, you go after individuals in the study who have serious conditions, headaches five times a week or something like that.

If you establish with the clinical trials that the drug is effective for these individuals, then by extrapolation, or whatever you want to call it, you say that individuals with less severe conditions can, in fact, also take the drug without having to produce new data.

Are we talking about the mechanism of action that you've described and so forth? Are we talking about possibly that type of situation that the chronic data and the mechanism which you say is involved here that would allow us to have comfort that, in fact, it can be brought down to acute conditions?

I realize there's some that are triggered by foods and what have you that might be different in terms of the general type of statement for labeling and for these questions we have to face.

DR. WILKIN: The answer is yes. I mean, you're saying essentially that if it's acute urticaria and you know it's acute urticaria that it should respond in the same way as patients who have the diagnosis of chronic urticaria or chronic idiopathic urticaria.

I think where the catch comes is is there a greater chance for a patient to make a misdiagnosis of self with short-term kind of urticaria as opposed to something that has been seen by a physician and labeled chronic idiopathic urticaria. That's where

the struggle is on this.

I don't think -- one of your colleagues mentioned that it doesn't seem that the scenarios that are playing out for the differential of acute urticaria have things that really would be made worse by non-sedating H1 antihistamines. The whole notion is one of delay.

Many of the things that we're talking about that would be really worrisome and you wouldn't want delay to occur, some of those are going to be things that occur perhaps more often in a medical setting. The really world class anaphylaxis is very often associated with parenteral antibiotics, penicillin, cephalosporin.

The radio contrast materials can lead to something that looks very similar and doesn't often have the immune system involved so it's called an anaphylactic kind of reaction. Really the reactions that occur within seconds are going to be of a medical variety.

There are some that can occur outside the medical setting. There can be insect things,

hymenoptera, stings that can lead to very rapidly developing anaphylaxis. Many of the patients who have anaphylaxis will actually develop their anaphylaxis over a somewhat more prolonged time period. I can't imagine that this would adversely affect a patient to have the H1 non-sedating antihistamine.

In fact, if they get to the point where they start having some swelling inside the mouth and the throat and they feel they are getting short of breath and they hop into the car and are driving down the road to the emergency room, it might be more beneficial to be on a non-sedating than a sedating antihistamine. In general, I think it really the things that are chronic idiopathic urticaria they have the same pathophysiologic mechanism.

DR. D'AGOSTINO: I'm concerned, as everyone else is, with the two wishes of the efficacy and the safety. The question I was addressing was in some sense the efficacy part that do we have enough data to feel that we don't necessarily need to do more.

I think the delay issue was certainly

before as the safety issue but, in some sense, it would be nice if we would not separate them but there is an efficacy issue. Do we really have to run acute studies? You can run acute studies.

I would be happy to design a study for you. I'm sure I could do it but do we really need to given the database we have. Then the second question is about the delay for the safety implications which you are addressing now.

DR. WILKIN: I think it comes back to what do we gain from the acute studies versus the resource intensity and what one might actually -- how one can extrapolate. First of all, of the acute urticaria patients that I most recently saw, and this was at Ohio State University, so we had three sources of urticaria patients.

One would be those who had really severe urticaria that bothered them enough to go to the emergency and they would often be treated at the emergency room before they would send them over to our gun clinic. They would get the systemic corticosteroid, parenteral, diphenhydramine, perhaps

some other sorts of things. That was one group.

Then we had the clinic at the campus was on the bus line so we had a lot of indigent patients that would just come to a walk-in setting. Typically they had urticaria the day before, but you wouldn't see it that morning.

Then the other place we saw patients was out in one of the tinier suburbs of Columbus, Ohio, Dublin, Ohio. There we treated diseases of the insured. They would often go through a family practice doc or an internist before they would come to us. It was actually rare in my experience, and I've seen a lot of patients who had urticaria, but to actually see urticaria at the time they are coming to the clinic visit so it's a little different.

I mean, those folks come in and they have croup when you're seeing them. I still think this is a very tough group to study. Hopefully you find some who have a history of food intolerance and you could recreate an acute episode of urticaria in the laboratory but undiagnosed they would be chronic. I mean, it gets back to what you mean.

I think the real fundamental piece is that all of the different ideologies that ultimately lead to the weal and to the itch do so by acting on the mass cell. It's the same vesical that's released in every single instance and it leads to the same itching, c-fibers, superficial dermis, and the same kind of weal because that superficial vascularplexis becomes leaky. I think it's one common mechanism.

DR. CANTILENA: Okay. Thank you.

Dr. Temple, Alfano, Dykewicz.

DR. TEMPLE: I don't know if this will reassure Ralph or not. We can't agree to labelling unless we believe there is substantial evidence that the drug is effective for what it's labelled for. One way or another perhaps by reference to other closely related diseases or whatever, we are going to have to reach that conclusion.

We've asked you what you all think about it and that will help but we have to under law reach that conclusion. We have no choice. We'll have to do it. If we can't reach that conclusion without another trial being designed, then somebody is going to have

to be smart enough to design another trial. The question is, and you just heard Jonathan address this, you may not need to do that. You may know enough already.

DR. D'AGOSTINO: That is obviously what I was trying to flush out.

DR. TEMPLE: No. It's a perfectly good question and we may have mislead you slightly by the question. We have to be convinced one way or another that there is something called substantial evidence which means it has to come from well controlled studies and then we'll argue about the applicability of whether it's really the same disease and so on. Those are things you have to argue about.

I wanted to follow up on one safety matter that Jonathan mentioned also. I mean, the nightmare here is that somebody is gulled by the availability of this drug when he wasn't gulled by the availability of the sedating antihistamines all these years into delaying treatment for his anaphylactic shock.

I would be curious whether other people agreed with what Jonathan said which I'm going to say

was my impression, that other things being equal, even if you're going to the emergency room, you are probably better laying down a little antihistamine base before you do it. It can't hurt and you won't attach more while you're waiting. Probably the odds are you will be better off if more people use this if they are about to develop something really nasty.

DR. D'AGOSTINO: Before that gets responded to, the question I was -- part of the question I was raising is we do have studies. There were studies that were done for the Rx. Is it possible in the appeal to the database that we appeal to those in terms of then an extrapolation?

DR. TEMPLE: Yeah. That's what I was trying to say.

DR. D'AGOSTINO: I just wanted to make sure I understood.

DR. TEMPLE: There's plainly some judgement involved in whether the situations are close enough for that to be relevant. We have written documents about how to go with one study or no studies or multiple studies. Those would all have to be part

of the consideration and the advice of experts figures into those considerations.

DR. CANTILENA: Okay. There's just a quick comment here from Dr. Sachs and then we'll go back to Alfano, Dykewicz, and then --

DR. SACHS: Just an important clinical point about anaphylaxis. The treatment for anaphylaxis is adrenaline or epinephrine. Giving an antihistamine doesn't actually treat anaphylaxis. I don't know that -- I mean, as long as giving the antihistamine didn't delay the seeking of treatment, it wouldn't affect the course but it certainly doesn't really help it.

DR. WOOD: But it doesn't make it worse.

DR. SACHS: If it delays the treatment, it makes it worse. If you look at anaphylaxis studies, particularly in kids where the kids died where the kids that got antihistamine and didn't get epi.

DR. WOOD: But that was in a hospital setting.

DR. SACHS: That's part of what led to have epi pens in schools and things like that was to

make it more available. That's just my point. You need the epi. That's all.

DR. WOOD: No one is arguing with that. The issue though is do we -- the real question is do we visualize that people with anaphylaxis because of this drug, because a non-sedating antihistamine is on the market, that people are going to rush down to Walgreens to get themselves a non-sedating antihistamine and, therefore, delay their access to epinephrine which they would not have done with a sedating antihistamines. That seems to me fundamentally improbable.

So, I mean, the issue is not does epinephrine -- is epinephrine the treatment for anaphylaxis. Clearly it is. The issue though for today's discussion surely is will marketing a non-sedating antihistamine over the counter prevent patients getting epinephrine. I think the answer to that is no.

DR. CANTILENA: Okay. Dr. Alfano and then Dykewicz.

DR. ALFANO: Yes. I didn't realize that

when I raised my hand the seqway would be so appropriate. I wanted to sort of offer two comments on anaphylaxis. One, at least some bee sting kits include diphenhydramine tablets as a sort of prelude to the more definitive epinephrine treatment as an event unfolds. At least one manufacturer sort of deemed it appropriate to put together a kit in that fashion.

The second comment relates to the fact that a comment earlier from this morning was suggesting that perhaps there should only be -- if this does go OTC there should only be one put-up. This becomes, I think, a great debate topic and you could pick either side.

I kind of come down on the side that a second put-up is advantageous because it makes the product visible and available to individuals who are suffering from CIU in a way that they have access to a non-sedating antihistamine. It would be the first time, I think, in which a proper label is available for these indications -- for that indication over the counter.

They are going to the counter now and they are acquiring sedating antihistamines and they are not labeled in the fashion that would warn a consumer about the risk of anaphylaxis. This product conceivably would be the first to be properly labeled.

The third issue is it would be shelved in this skin irritation section where someone who has these chronic conditions would likely see it and pick it up and read it. The other way it's just going to be in a wrong section of the pharmacy.

DR. CANTILENA: Okay. Thank you.

Dr. Dykewicz and then Dr. Szefler.

DR. DYKEWICZ: Well, several comments on this specific issue about anaphylaxis, delay in treatment, risk for fatality, rapidity of onset.

First of all, maybe just to return to some comment that were made earlier, it is certainly true that anaphylaxis can occur in medical settings due to use of parenteral medications, antibiotics, radio contrast media, but what we're looking at really in a nonmedical setting would be the risk of anaphylaxis from foods and potentially certain oral medications,

maybe even including aspirin and nonsteroidal anti-inflammatory drugs with the pseudo-allergic reaction that was addressed earlier.

It has been found in some studies that food induced anaphylaxis can be more problematic to treat. The reason is that because there is some time delay in the onset of the symptoms and the progression of the symptoms by virtue of the requirement for a need for oral absorption that, in fact, fatal food anaphylaxis can have a slower onset, a slower progression, but still lead to fatality.

If we're getting at the questions that have been raised earlier about whether somebody would run down to the local drug store and because at that point the person is only having hives and they pop a tablet of a medication which now has over-the-counter indication for hives, there would be the possibility that would, as Dr. Sachs brings up, prolong or delay the patient seeking medical attention and thereby delay the administration of epinephrine and thereby cause a greater risk of fatality. If you're going to go the whole nine yards, that is a scenario.

The other thing, though, about the kits that are commercially available that do have antihistamines in them, actually it's chlorpheniramine with epinephrine in a kit, it is certainly appropriate to use antihistamines in the treatment of anaphylaxis, but that is always viewed as only an adjunct to the primary treatment with epinephrine.

Any type of scenario in which someone would delay receiving epinephrine, whether it's use of an antihistamines with over-the-counter indication or not, that would result in fatality or greater risk thereof.

DR. CANTILENA: Okay. Dr. Szefler, then Dr. Joad, then Dr. Davidoff.

DR. SZEFLER: I guess I just want to clarify a few points. Because the package inserts change so much I haven't read every one or do I read every one. Let me just get it clear in terms of loratadine. It is approved in the package insert for chronic urticaria. Is that right? The studies that were done were deemed sufficient.

DR. CHOWDHURY: Chronic idiopathic

urticaria.

DR. SZEFLER: Okay. So the discussion that we're having is not about the indication for the disease. It's about sharing the information and putting it in the product. I mean, why would you not want to put information in terms of its approval? I guess may Dr. Ferguson's talk crystallized that for me.

What reason would you not want to put the information in there other than maybe the misinformation about other urticaria? I mean, it's like sharing information that is reassuring the patient that they have been receiving adequate treatment.

Maybe I just missed that point in the whole review. I didn't have a package insert on hand but if it's there already, it just seems like it's a logical transfer of information. It's not new information. It's a logical transfer of information.

DR. CHOWDHURY: To answer the question and to address the point here, the studies for loratadine and most other new antihistamines were done on CIU

patients. The application that we reviewed we hadn't had where to get the indication of CIU. There were no acute urticaria or other studies for these antihistamines.

DR. SZEFLER: But it is approved for chronic idiopathic so it's already there. It's not like we're discussing the approval.

DR. CHOWDHURY: Already approved and marketed with the indication of chronic idiopathic urticaria.

DR. SZEFLER: Okay. So my second question is --

DR. GANLEY: Can I just add something to that? If you put it into the package insert, you are in essence giving it as an OTC indication. The company can have an add-on tomorrow for direct consumer labeling for their prescription product to go see your doctor for your urticaria. It's not that we're withholding information from the public. All this is public information. Anyone can go get the package insert. They are readily available.

DR. SZEFLER: But the patient still kind

of deems the responsibility of treating themself even though it's a medical disease.

DR. GANLEY: If you start putting uses into a package insert that's labeling. If it's an OTC product, you are essentially giving it an OTC claim. I think that's what the issue is here. It's not that we're trying to withhold that.

I'm not sure if people -- there is some confusion abut that but if this was not an OTC claim it would still remain a prescription claim. It's not that the FDA is taking something away from them.

The issue is if allergic rhinitis becomes an OTC claim, should this also become a OTC claim? If it doesn't, it remains a prescription claim. They can still market the product as a prescription product and do their direct-to-consumer advertising.

DR. SZEFLER: Maybe this gets to the root of a problem and maybe I'm just not clear on payments. I'm trying to figure out who this benefits and how it might be used to benefit.

Suppose I'm a patient and I go in and I see a physician and I have chronic idiopathic

urticaria. I have medical benefits. The physician feels that the most appropriate drug for me is loratadine and then tells me, "For the next year go out there and purchase it on your own." I bear the cost.

On the other hand, if it's not on the label, can the physician then say, "Your best drug is loratadine. Because it's not in the label it's a prescription and, therefore, your insurance company should pay for this." Is that what it boils down to?

DR. GANLEY: I'm not sure we factor that into our decision as to whether this is an appropriate indication for an OTC setting.

DR. SZEFLER: It is for the patient.

DR. GANLEY: I understand but this came up at least year's meeting, I think, and we don't factor that into the decision process. I suspect we could get by with --

DR. SZEFLER: I guess I would like to factor it in.

DR. GANLEY: You're welcome to do that but we don't factor that into our decision. I think some

of the issues, I don't know what individual's co-payment is for prescription products. Mine is, I think, $15 a month unless I get a three-month prescription. There's still some co-payment on the side of a consumer in most cases, even if they have a prescription plan.

DR. SZEFLER: I guess I have to sort out the issues.

DR. GANLEY: It's what can we factor into that decision and that's generally not been a factor.

DR. CANTILENA: Dr. Temple, do you have a comment before we go to the next one?

DR. TEMPLE: Yeah. I mean, as I'm sure people are aware, there are a number of drugs that are available where the same new molecular entity or the same actimority (phonetic) is available both as an over-the-counter drug and as a prescription drug.

Ibruprofen, for example, remains as prescription Motrin in doses -- in tablet sizes above 200 milligrams. Nothing stops a physician from prescribing it that way in which many people will cover it or telling someone to go get it as an over-

the-counter drug in which cases I understand most of the time will not be covered. We don't deal with that.

But in case you have any doubt about whether most Ibruprofen is used as an over-the-counter drug, try to find the labeling for Motrin in the current PDR. You won't find any Rx Ibruprofen labelling. People can do what they want with that. The question here is only suitability of a particular claim for over-the-counter use.

There are specifications for what makes a drug suitable or a claim suitable for over-the-counter use. You have to be able to diagnose it, manage it, and so on. That's why we worry about each of the claims individually. Before you put it in OTC labeling, you have to believe -- usually we have a way out of that, too -- you have to believe it can be used by the individual that way.

There is such a thing as professional claims for over-the-counter drugs. Aspirin has professional labeling where you are absolutely positively supposed to go see the doctor to get your

cardiovascular disease prevented. Does that always happen? We don't know.

DR. CANTILENA: Okay. Dr. Joad and then Dr. Davidoff.

DR. JOAD: I wanted to speak to the general indication of hives and whether the evidence we have so far about the use of antihistamines in this specific CIU is sufficient for us to approve it or have packaged labeling for acute hives.

I would argue for evidence based medicine on that. That is a big number of patients in comparison with the CIU patients, No. 1. Secondly, I think you could make an argument that is a theoretical one that antihistamines and CIU are there present all the time occupying those H1 receptors so that they are not available for the release of antihistamines.

Whereas, in acute hives if it's really a single hit one especially, the event will have already happened. The histamine receptors will be occupied. The secondary effects are already well underway. You may not be able to go back with an antihistamine and reverse that.

There's no reason to say I'm right particularly but if you don't do an evidenced based study of what really happens for acute hives, I don't think you know the answer to that. I think Dr. Sachs is telling us that primary care physicians are seeing people with acute hives and they could be studied in a primary care setting.

DR. CANTILENA: Dr. Davidoff.

DR. DAVIDOFF: Just to stress that last point, I agree. I think it would be perfectly doable to design an appropriate study for studying acute hives. I actually had a question, though, that had to do with the presentation Dr. Engle made about pharmacist involvement in guiding patients about taking over-the-counter drugs.

I think that is a very important point since it does say in the footnote that 61 percent of the respondents in one survey said that they did use over-the-counter drugs at one or another type of pharmacy.

That raised a question in my mind as to how often that really -- the pharmacists really get

involved in interaction with patients at the time they purchase over-the-counter drugs. In the pharmacies I've gone into, most of the antihistamine type preparations are in an open display. They are not behind the counter.

If the person purchasing it wanted information from the pharmacist, they would have to go over to the pharmacist and ask them. The pharmacist is usually busy filling prescriptions so it is hard to get their attention.

I actually wondered if there are any data on how often pharmacists are actually asked about over-the-counter preparations because my suspicion is that it's actually not very often unless the drug is behind the counter.

That led to my second question which is -- it expresses my naivety in this, and that is is there any kind of behind-the-counter system in the U.S, formal or otherwise? I didn't think so. It certainly doesn't look like there is but I thought maybe there was. I do think there are such systems in some other countries. Am I correct? But not in the U.S.

My first question really is are there any data on how often pharmacists are actually involved in over-the-counter type purchases?

DR. CANTILENA: Okay. The answer to the second question is that there is not that category available in the United States and that I will ask our Drs. of Pharmacy of they would like to respond to your first question.

DR. JOHNSON: I am not aware of any specific data that describe how often individual seek pharmacy input. It's been a long time since I worked in a retail setting but I have worked in a retail setting and you do have a fair number of people who come and ask.

Typically it will be in the first time they would use such a product. Obviously once they've used it and are familiar with it, they are much less likely to come back and ask for that input. It's clearly a process that is driven by the patient seeking information.

There's nothing that forces the patient to see the pharmacist. I mean, I think there is a fair

amount of it and if the labeling on the box -- not on the inside of the carton but on the box suggest that they may want to consult a pharmacist, I think that might increase it.

I mean, there are a couple -- we do have a few drugs that are, in a sense, behind the counter. Insulin, for example. In some states there are Schedule V compounds cough products that have codine, for example. In general we don't have that category that some other countries do.

DR. DAVIDOFF: Well, could I ask in connection with that on the last point you made, are there examples of over-the-counter medications that say on the box that you should consult your pharmacist as well as you should see a physician in certain circumstances? Are there any examples of that? It seems to me that could be very constructive.

DR. WOOD: Well, there are data from the UK behind the counter prescriptions. The data say that almost uniformly no advice is offered. The drug is actually behind the counter and the person goes up to the counter, asks for the drug, and it's passed

over with no advice being offered.

There are also data from this country offering advice on prescription medicines and the frequency which that happens and there's very little advice offered on that. In fact, the majority of patients in surveys don't recognize that when they sign that form, they are signing that they are actually turning down the advice for prescription drugs. There's actually a lot of data on the advice for prescription drug issues.

DR. UDEN: But pharmacists are the -- they are there and are available to be consulted with if, in fact, there is -- and labeling might take care of it. I know in TV ads you consult your doctor or your pharmacist but I don't think that there's any OTC labeling which does that. I won't make my next comment.

DR. CANTILENA: Are there examples, Dr. Ganley or Dr. Katz?

DR. KATZ: The new drug facts on labeling actually does have specific headers that will advise a consumer to go seek their physician or healthcare

provider or to go ask the pharmacist. It's very specific and has listed bullet points underneath.

Some may be related to asking for information regarding other concomitant medications or concomitant medical problems that someone may have so they shouldn't take the problem together. We'll say ask a doctor or pharmacist in certain headers. In others it will say just ask your doctor or healthcare practitioner.

DR. CANTILENA: Okay. I think actually what I would like to do now is just take a 15-minute hiatus here from this interesting discussion and have everyone come back in 15 minutes. We'll clear up any other questions and then we'll go to our questions. Thank you.

(Whereupon, at 3:12 p.m. off the record until 3:25 p.m.)

DR. CANTILENA: Before we go ahead with questions, Dr. Monroe has asked to clarify a point on the question on anaphylaxis for the sponsor.

Dr. Monroe.

DR. MONROE: Thank you. I'd just like to

make a couple of very brief comments on the issue of safety. The first has to do with anaphylaxis. I think there is consensus that it's a rare situation. Antihistamines are not the treatment of choice. Epinephrine, adrenaline is.

An issue was brought up would the approval of an agent like loratadine OTC create a sense of complacency that might cause added delay in the consumer seeking appropriate care. I think the best answer I can give is that we've got 10 years of experience in Canada and the UK where this is an OTC medication and there's no indication of increased incidence of complications or deaths related to this condition. We appreciate it's rare. It's a serious thing but we don't think that making loratadine OTC would in any way change in a negative fashion the status quo.

I would also just like to say on safety I think that the lack of approval of such an effective and safe agent as loratadine OTC would create the maintenance or the perpetuation of the status quo where most patients who have urticaria, the spectrum

of urticaria, that's the vast majority of people with acute and some with chronic who now access the only OTC medicines that they have.

They are accessing sedating antihistamines that are far from safe. I don't think you should underestimate the potential harm in the perpetuation of those people who right now, and it's the majority of people with hives, access care through a sedating much less safe medication than loratadine.

I would also say there are subsets of the current population, particularly the elderly, who are taking these medicines and they are more than antihistamines. They are anti-colonurgics (phonetic). They affect urinary retention. They affect glaucoma.

I think if you're looking at patient and consumer safety, the movement of this drug, Claritin, to the OTC scenario, I think, creates a much greater improvement in the safety equation than not doing it.

DR. CANTILENA: Yes, Dr. Davidoff.

DR. DAVIDOFF: Just a quick point in connection with your first issue. Absence of evidence is not the same as evidence of absence. It seems to

me that unless someone has specifically gone and looked at the fatal cases of anaphylaxis in over-the-counter countries to see whether or how often the availability of the over-the-counter antihistamine might have, in fact, delayed treatment, I don't think you can say there is any information one way or the other on whether this availability in those countries has delayed treatment and contributed to fatalities?

DR. CANTILENA: Dr. Uden.

DR. UDEN: I just have to take this opportunity to remind us that 11 months ago these drugs weren't safe enough to be OTC and now they are. It's quite a reversal.

DR. CANTILENA: Thank you for that historical point.

Dr. Clayton, are there any other issues that you wish to clarify from the discussion that was not absolutely clear? Okay. I just actually have a question for Dr. Ganley. As we go through the packet we're looking at in essence a switch application because it's already an approved Rx indication.

I guess are there examples in your files

that I'm not familiar with where we have actually accomplished a switch recommendation without an actual use study with the use of the Internet, I guess, as a survey of consumers. Is there anything that you can point to in the files that we have experienced in this area?

DR. GANLEY: I think there have been. The vaginal antifungals actually did not have an actual use study but I think there are probably other applications that have never made it to the committee that we haven't required actual use studies on.

Clearly when the discussion occurred last year -- the committee meeting occurred last year regarding allergic rhinitis, we had actually come out on the positions that we didn't think it would need an actual use study because it's a category of drug that is already available OTC for this indication. I think there are examples where we don't require that.

I think the issue with the consumer surveys is what kind of -- with that type of study what is the value of that study. Is that a study that helps you design a better label comprehension study

because you understand a population's perceptions of how they should use certain products, or should it be used to improve the design of an actual use study or things like that.

Again, I go back to what the questions in this population they were actually asking. I didn't really need that study to be convinced that someone who had gone to a physician and had been told they had chronic urticaria and was instructed to use a specific product.

They wouldn't do it necessarily correctly had all these steps in the physician/patient interaction occurred. You could take many diseases that have intermittent symptoms where this would occur. Migraine headaches where there is something prescribed to a person and they are told to take it when they have a severe headache because they already know what their migraine is like.

A patient with anginepectoris (phonetic) who is given sublingual nitroglycerin, most of them know when to use that correctly so you don't need to do a study to tell me that someone that has a

diagnosis of CIU would be able to use this product. But that's really not the major issue here. I think it's how is the general population going to use this product.

The question with the surveys, I think, is this type of study that the committee would like to see come in supporting applications that would limit use to a specific population, or should it be some type of study that is used to -- I think Dr. Davidoff had mentioned earlier we don't know what the general -- how the general population is going to use this.

I may have been better to survey them and see how they use these products and then try to create a label because clearly I think there are issues in the label comprehension that even the way it was written that the cohorts in the general population and the acute hives population they weren't going to use it as it was labeled. Could that consumer survey have been better used to create a better label?

DR. CANTILENA: Okay. Thank you. Are there any other specific issues that the committee would like to discuss before we go to the questions?

Any other pieces of information?

Dr. Sachs.

DR. SACHS: The one question I have is what age is this supposed to be approved down to?

DR. CANTILENA: Dr. Ganley. Is it 12 and above or six and above?

DR. GANLEY: I think it was about six years of age.

DR. CANTILENA: Okay. Any other questions?

Yes, Dr. Rosenberg.

DR. ROSENBERG: Just without harping on this just to say one more time that the patient will do one of three things. They will either seek medical care and get it at a physicians office, they will buy what is presently available over the counter which is sedating, or they will go to a health food store and go to that sort of thing. These are the only options.

I turn again to that chart on Tab 7 that shows the preferred treatment, No. 1 choice of so many physicians is corticosteroid. In the material that we were sent there are these review articles and I've

reviewed textbook articles. Malcolm Grave says use a non-sedating antihistamine once in a while.

Anytime you're on a consensus committee you always have to say something. Everybody is afraid they are going to be sued unless you make it okay to put everything else in. What they really say is try the antihistamine.

Then there's a statement from another consensus from Europe. Then there's another authority and a book on urticaria that I've always found the most sensible one. It's an older book by Dr. Champion from Britain who is one of the original editors of the Rook series of that major textbook.

He wrote a whole book about urticaria and he concluded that after this and that and trying your best, he said the best thing to do for these people is interdict aspirin and try to find an antihistamine that will give them some relief without putting them to sleep. We have that here now.

I think truly there are hard cases but if the people do this first and then go to the doctor if they didn't get better, then prednisone and so forth

is okay, I mean, if they're that sick and maybe they are going to get a workup but they're sure getting an awful -- too much of it now in my opinion.

I see cases. I mean, I've testified for a plaintiff and a fellow you had urticaria didn't want to miss work so he stopped at the emergency room on the way to work in Honolulu every two weeks for a refill of his dose back. He had urticaria and he had aseptic narcosis of the hip.

Another patient who has just been referred in because of generalized coccidioidomycosis to our infectious disease fellow. It was a dermatologist who made the diagnosis and he called me and said, "You don't want me. You want our infectious disease guy."

I saw him and I said, "Did that fellow come in from Jonesboro?" He said, "Yeah." I said, "Does he have AIDS?" He said, "No, he doesn't have AIDS. Somebody has been giving him 40 milligrams a day of prednisone." Thank you.

DR. CANTILENA: Okay. Dr. Ganley.

DR. GANLEY: I think the one thing about if you're talking about the physician survey and the

first line therapy, I think you have to -- there's details missing there where you can't really figure out what's going on there unless you ask more questions.

It may be that many of these individuals who come in have already tried multiple antihistamines and they have failed them. We don't know that. If you ask follow-up questions to those questions and get the details, that may be the bias of that physician because 95 percent of the people who come in with chronic urticaria have already tried diphenhydramine and chlorpheniramine and they just didn't work.

I don't know how much to place on that. I think the issue that you make that's valid is that we should be advocating these as first line therapy. The question is how best to do that. Is it narrowing this claim down or is it having a more broader claim, for example, if it's to go OTC.

DR. CANTILENA: Okay. Thank you. Any other comments before we move to the questions? Very good. What I would like to do then is actually go around. We'll start with question No. 1. What we'll

have you do is indicate your vote, yes or no, and then comment if you would like to comment. For the first question, "Is urticaria a disease process appropriate for an OTC indication?"

Actually, we can start on that side of the table. Dr. Alfano, you can comment but, unfortunately, you can't vote. If you would like to start with your comment if you have one. If not, then we'll just head around the table with our vote and comment.

DR. ALFANO: Yes. I believe it is an appropriate indication.

DR. D'AGOSTINO: Dr. Dykewicz.

DR. DYKEWICZ: I'm going to vote no because, at this point in time, I don't believe we have sufficient use studies to be assured of how this is actually going to be used in practice.

I say this though with kind of a divergent view in my sole, and that is I think we do recognize that there's a problem with the urticaria as it currently exist. I agree that the de facto use of the currently available over-the-counter antihistamines

with their sedating properties is undesirable if it were in an alternative way available for the patient to get a non-sedating antihistamine that would be effective.

I guess my dilemma as I've tried to express during the course of these meetings is what can be done to educate the patients so that they would use these medications most appropriately and minimize risk to them.

It occurs to me that the efforts to provide appropriate labeling on the package might actually be a very good educational thing for the public and if the public were to adhere and to follow the recommendations that are listed on the label, that would be a good thing.

I think if anything there is probably both among physicians and among patients an under-recognition of the potential seriousness of urticaria sometimes being an indication of a serious underlying disease. There may be too much of a kind of cavalier approach to it where you just give some antihistamines and don't worry about the full workup of it.

Although I do vote no, I think with some additional use studies, one might be convinced that this, in fact, would be a good thing to have available and, if you will, even give the opportunity to gain greater education for the public.

DR. CANTILENA: And just as a point of clarification, when you say use studies, you mean actual use studies where they can buy it like in the pharmacy?

DR. DYKEWICZ: Well, I'm not really clear on whether there would be some type of -- the thing about surveys versus where they would actually be using it, I think once you actually would approve it for over-the-counter use once the horse is out of the barn, you probably can't come back very readily with that I would think.

I guess some sort of limited use studies maybe where people would be given the opportunity to obtain the drug in limited circumstances as part of a study group.

DR. CANTILENA: Yes. Actually, those are called actual use studies. Go ahead.

DR. GANLEY: Yeah. I think his answer is then yes, that it could be an OTC indication but you need these types of studies. I tried to point out earlier if you're answering no, you're coming to the conclusion that this never -- there's nothing that the sponsor could do that could actually convince you that this could be an OTC drug.

If you think this is a possible OTC indication, it would be a yes and then what kind of data would you be interested in seeing. If you say no, then that's shutting the door on anyone coming in for this indication.

DR. CANTILENA: So would you like to amend the wording of the question to be, "Could urticaria be a disease that was appropriate for OTC?"

DR. GANLEY: I'll leave it to your discretion.

DR. CANTILENA: I think that's what you're asking so why don't we actually amend the question, "Could urticaria be a disease process appropriate for an OTC indication?" Your vote, Dr. Dykewicz?

DR. DYKEWICZ: With all the caveats that

I've stated, then I could state yes.

DR. CANTILENA: Thank you.

Dr. Joad.

DR. JOAD: I vote also yes, that it could potentially be OTC. I would recommend that it be broadened to all reasons for urticaria due to the things we mentioned about, that it would be impossible in practical terms limited to chronic idiopathic urticaria.

Then the studies I would like to see would be a study that shows people recognize hives versus other important things that could be mistaken for hives in a study of efficacy, an outcome study of efficacy and acute hives and studies in children.

DR. CANTILENA: Okay. So we've actually -- we've had you cover actually question 1 and 1A.

DR. JOAD: And 2.

DR. CANTILENA: I've chosen to ignore that response because it's out of sequence now. Just kidding. If we can actually go back to Dr. Dykewicz for 1A and actually what we'll do is if you answer yes for 1, then you can also answer 1A.

DR. DYKEWICZ: Well, should the indication be for chronic idiopathic urticaria? Potentially yes with the caveats. Should it be broader such that it includes acute urticaria hives? Potentially yes but my caveat to the FDA would be I think it would be much more difficult to gain confidence about the appropriate use of this medication by patients then it would be under the very restrictive provisal of chronic idiopathic urticaria. I'm saying yes, but hear all my caveats.

DR. CANTILENA: Okay. Thank you.

Dr. Szefler.

DR. SZEFLER: I would vote yes. I don't know how you do it but I would like to see studies done with acute urticaria. Again, as I said this morning, I think if people really sat down and thought about it in terms of primary variables and conditions to study it, and I think it's feasible, then I would like to see those put into the package so that it rules out any of these considerations about inappropriate use.

DR. CANTILENA: So yes for 1 and yes for

1A?

DR. SZEFLER: Well, in 1A it's really a desire to see the studies. I think the implications of the study -- the implications of the question if I said yes to A would mean that I approve it right now for both.

DR. CANTILENA: Actually, the question is now could it be a process and, if it could, would the indication then -- should the indication be broader to include hives. Then we'll actually talk about the studies that you would like to see and others would like to see under question No. 2.

Dr. D'Agostino.

DR. D'AGOSTINO: Yes to both.

DR. CANTILENA: Dr. Krenzelok.

DR. KRENZELOK: Yes to No. 1. We certainly have an established indication. I don't think we have information to allow us to put the general urticaria statement on it but I think that post-marketing surveillance of off-label use could provide us with a wonderful opportunity to extend that indication sometime down the line.

DR. CANTILENA: So yes to 1 and qualified yes to 1A.

DR. KRENZELOK: Yes.

DR. CANTILENA: Dr. D'Agostino.

DR. D'AGOSTINO: I guess I'm really confused. This doesn't sound like a question that's directed to the product so why are we talking about the product? I mean, it's a question about the indication, isn't it?

DR. GANLEY: Yeah, it's about the indication because this company isn't the only company that is interested in this claim so if we have to give advice to other companies, it's important for us to understand what we should be telling them, that you need to go for a broader claim or you limit it to chronic urticaria.

Once we get over that hurdle, then looking at the data that Schering-Plough has submitted, does that lead to an indication in the OTC setting or do they need to do other studies? Should they go after a more broader claim?

So this is the more general question that

you have to overcome and it's mainly because we already have gotten inquiries from other companies that have antihistamines that have an interest in getting this claim.

Dr. Krenzelok's comments, I think, appear to be directed at the company's product and that's really question No. 2 where, you know, what do you think if you vote yes that this could be an OTC claim is it chronic urticaria, is it acute hives. That's where we need some input.

DR. CANTILENA: So if I understand you then, really question 1 is in general and question A is product specific.

DR. WOOD: Question A needs to be qualified because I don't people have a clear understanding of what we're voting for there. The question A as written must relate to the evidence that's been offered for a specific drug.

Clearly if you vote yes to the stem, then presumably other hives in any subdivision could be potentially approvable to provide data, but having the data has to relate to a product. The way it's been

modified doesn't make much sense unless we modify it again.

DR. GANLEY: Well, I guess it depends on what your priors are here, whether you think that this is already being used out there by the population in some respects.

DR. WOOD: Well, let's read it. What we've modified it to, as I understood it, was, "Is urticaria a disease process which could be appropriate for an OTC indication." That was the modified stem. Right? Then if yes, should the indication be for chronic idiopathic urticaria or should it be broader to include acute urticaria.

Well, these two subdivisions depend on -- are data driven and they are data driven depending on the drug that you've got in front of you so it's not appropriate as written like that. That's why the discussion each time raises issues related to the drug.

DR. CANTILENA: But I heard a lot of discussion actually that said that to have the indication just be CIU is actually confusing to the

consumer and it should actually just be hives. I thought we were actually addressing that by broadening it. I actually sort of see that as a general issue and not product specific.

Before we give you confusing advice, maybe we should get on the same page. Dr. Temple.

DR. TEMPLE: Each of these has multiple variations. One question you could ask is if you had the data for acute hives, would it be better to label it more broadly. That's one kind of question. I don't hear anybody thinking that wouldn't be good

Then there's the question of do you have the data to do that. There's been a lot of discussion one way or the other. Some people probably think they have the expert views to contribute to that but maybe not everybody does. As I said before, in the end we have to conclude that the data exist for that or we can't say yes. We can't legally say yes. I don't know if that helps.

DR. CANTILENA: Yes, a comment, Dr. Rosenberg.

DR. ROSENBERG: Can I speak to that? I

think that you were wise to broaden it because that was one of the things that, in fact, did come up and everything comes out more neatly.

On the other hand, the Schering company is asking for the chronic idiopathic urticaria and brought an exhaustive and complete search of this but not the other. The reference that I showed sites this as evidence based and had one reference.

I'm not going to be here tomorrow but other on this panel will be here tomorrow. We've got members of the panel from the Pacific time zone. I'm sure that one could come up with literature, a search done by an expert informationist that would help everybody by getting up in time tomorrow morning.

DR. CANTILENA: Yeah, I actually think we are sort of confined to this day on this agenda. I guess what I would like to suggest, and please, Dr. Ganley and Dr. Temple, if you're comfortable with us going in the generic sense as the overall indication could be.

Are we confusing you, Dr. Titus, in terms of the answer to 1A? Should we just go one at a time?

Overall I think their answer is clear with the following qualifiers. I think if you're okay, if the FDA contingent nods their head, I guess we will go forward as we are. I didn't say nod off. I said nod your head. Are we okay?

DR. GANLEY: I think the issue is that we have a claim that's -- you know, I think every prescription product has a claim for chronic idiopathic urticaria. I think Dr. Wood got into the discussion earlier about whether that should just be made a broader claim.

Do we have a comfort level of efficacy or should be segment it to that population and allow companies to either do chronic idiopathic urticaria or they could go after acute hives or they could subsegment it into any other population that they see fit.

I think that's where it was sort of directed at in general terms is that this is the claim on all of the prescription products right now. To carry it straight over is a choice, too, or should we ask -- should we try not to confuse consumers and have

some products labeled for chronic idiopathic urticaria and some labeled for acute hives or hives in general.

We would like to come up with some consensus as what to tell people as to what the label should look like. It should be similar, I think, potentially across the board unless someone has a differing opinion on that.

DR. WOOD: Could I offer a solution? Supposing we said that the indication would be hives after you had seen a physician? Would that deal with the --

DR. TEMPLE: Can I make a counter? Maybe this is what Charlie was suggesting. First cover the question of whether urticarial disease of some sort is suitable for over the counter. Get that out of the way. Then you can elaborate on what exact claim you like best. Knowing that urticarial disease is suitable for over the counter, the first thing is absolutely critical to us.

DR. CANTILENA: Okay.

DR. TEMPLE: The other is a refinement. Alistair's suggestion is certainly one to think about

as would a variety. Again, remember that we're going to have to be satisfied the data support whatever we say or whatever you suggest.

DR. CANTILENA: Okay. Just so we're clear on what everyone's intentions were, Dr. Dykewicz, Joad, Szefler, D'Agostino, and Krenzelok voted yes to question 1 as modified and yes to question 1A in the general sense, not product specific.

DR. D'AGOSTINO: I want to make it clear that I understood 1A to be as it's written and I voted yes on that. I think that we're talking about if you're trying to make it too segmented, it's not a very useful claim for OTC so I was answering the question as it was originally written. I believe I understood it correctly.

DR. CANTILENA: Okay. The other four individuals voted yes. Let's continue.

DR. GANLEY: Lou, can we just get the answer to No. 1 and then go back and just --

DR. CANTILENA: Let's do 1 first.

DR. GANLEY: Don't take a vote on 1A of yes or no. Just let me put their comments on the

record because that's actually more important and we can sort of swift through that.

DR. CANTILENA: So you want their comments while they're voting?

DR. GANLEY: It's easier to go through one and just give a yes or no and then go back and get the comments on 1A.

DR. CANTILENA: So the attempt to expedite things, I guess, didn't work out exactly as planned. Okay. The first five have voted yes to one. Dr. Uden, question 1 as modified.

DR. UDEN: Yes to 1 and I'll comment on 1A when appropriate.

DR. CANTILENA: Thank you very much.

Dr. Johnson.

DR. JOHNSON: Yes.

DR. CANTILENA: Dr. Lam.

DR. LAM: Yes.

DR. CANTILENA: Dr. Davidoff.

DR. DAVIDOFF: Yes.

DR. CANTILENA: Dr. Gilliam.

PARTICIPANT: He's out.

DR. CANTILENA: Dr. Gilliam will be back.

Dr. Sachs.

DR. SACHS: Yes.

DR. CANTILENA: Dr. Wood.

DR. WOOD: Yes.

DR. CANTILENA: Dr. Williams.

DR. WILLIAMS: Yes.

DR. CANTILENA: Dr. Clapp.

DR. CLAPP: Yes.

DR. CANTILENA: Dr. King.

DR. KING: Yes.

DR. CANTILENA: Dr. Rosenberg.

DR. ROSENBERG: Yes.

DR. CANTILENA: Thank you. Let's go back around for question 1A as written if yes for the general condition not product specific, should the indication be for CIU/Hives or should it be broader such that it includes acute urticaria/hives. We're broadening it beyond CIU. If I may, Dr. Dykewicz, Joad, Szefler, D'Agostino, and Krenzelok have voted in the affirmative yes.

Dr. Uden, 1A.

DR. UDEN: Broader, yes.

DR. CANTILENA: Should it be broader or should it be restricted?

DR. UDEN: I think it should be broader and I find it real interesting that we are using the product that might be going nonprescription as the battle ground or the proving ground for acute urticaria. It has not been done with prescription drugs before.

DR. CANTILENA: Dr. Johnson, should it be CIU only or should it be broader?

DR. JOHNSON: My feeling is that it should be broader and there's a couple reasons for that. One is really sort of reality based, and that is that's how patients are going to use it. Everybody with urticaria is going to use it.

The second as it relates to data, I mean, I think, you know, in this perfect academic world it might be nice to see data. But I guess I am comfortable where we are because at present to say these agents are not acceptable for acute urticaria means that we don't believe that all the consensus

bodies and experts in dermatology know what they're talking about.

Apparently all of them recommend this as the appropriate therapy and the pathophysiology of the process suggest that is appropriate therapy. I guess I feel comfortable that the information we have is appropriate for broadening without actual use kind of studies.

DR. CANTILENA: Dr. Lam.

DR. LAM: Yes in a general sense.

DR. CANTILENA: So yes, it should be broader?

DR. LAM: Um-hum.

DR. CANTILENA: Dr. Davidoff.

DR. DAVIDOFF: Possibly. I don't want to say an absolute no picking up on Dr. Ganley's concern about what absolute no means. I don't understand what he means by that because I can't see how a no is ever absolute. It seems to me there would always be the opportunity to bring back new information that would open the door again but that's another discussion.

The reason I'm hesitating is I'm somewhat

impressed with Dr. Dykewicz' comments about concerns about anaphylaxis. I think it would be feasible to gather information from the other countries that have had OTC non-sedating antihistamines to see -- to look at their cases of fatal anaphylaxis and try to get a direct body of information on whether or not there's been a contribution to delay and perhaps to fatality.

It seems to me that the likelihood is that there will either be no evidence that that happens or it will be very, very minimal amount, but at least the decision would have been made with their eyes open instead of doing it in the dark. As it is now, this would be a decision, yes, to broaden it but made on the basis of really no input. I think it's not good for the public health and it makes everyone in this room rather vulnerable.

I also think I would wait until there had been some search for the data. Possibly there are data on management in acute anaphylaxis. An exhaustive search would be very helpful. That could be done fairly quickly.

I would also like this information on how

often acute hives is, in fact, misdiagnosed by self-diagnosis. It seems to me that's information that may not be critical but it would certainly be very, very reassuring to have that information before there was a decision made to broaden the indications.

DR. CANTILENA: Thank you.

Dr. Sachs, broader or CIU only?

DR. SACHS: Actually, I also agree with broadening the indication with the caveats that have already been raised.

DR. CANTILENA: Thank you.

Dr. Wood.

DR. WOOD: I would like to see us remove idiopathic which I think is meaningless to most individuals. Remembering this is an indication for an over-the-counter drug it needs to be understandable to patients. I would argue for making it hives, removing urticaria.

If we say the indication is hives after you've seen your doctor and he or she has made that diagnosis, then essentially we avoid the problem of misdiagnosis, at least for the first episode, which

is, after all -- and it also fits with the indication that the sponsor is seeking. Secondly, given the time it takes to see a dermatologist, some might have many acute urticaria patients in there anyway.

DR. CANTILENA: Thank you.

Dr. Williams.

DR. TEMPLE: Lou, that was actually a do not broaden it. You want to change the name but you don't want to broaden it.

DR. WOOD: No. The indication would be hives.

DR. TEMPLE: Oh. Hives after you've seen your doctor.

DR. WOOD: Right.

DR. TEMPLE: I see. So that's something different. Okay.

Dr. Williams.

DR. WILLIAMS: Yes and broader.

DR. CANTILENA: So the indication should be broader to 1A?

DR. WILLIAMS: Yes.

DR. CANTILENA: Thank you.

Dr. King. Excuse me. Dr. Clapp.

DR. CLAPP: Yes to broaden it and my reasoning is for many of the caveats shared previously, but also because of the basic responsibility I think we have to consumers and patients to adequately inform them of appropriate usage of a medication rather than to narrow down the spectrum of using to add further confusion to a medicine that they will likely use anyway.

DR. CANTILENA: Thank you.

Dr. King.

DR. KING: Yes, should broaden it. I would like to see two things happen. One is I would like to postmark the surveillance simply to come after the data because I think we need to know how many may have had delay in diagnosis or complications.

There's data out there from the European group and also probably from the occupational health groups. I think we're just looking in a darkened alley here and we need to find out more in that area so broadening it would get us there with public education.

DR. CANTILENA: Thank you.

Dr. Rosenberg.

DR. ROSENBERG: Yes, broader.

DR. CANTILENA: Broader. Okay. My vote was on 1, could it be, yes, and on 1A, broader. We're still missing Dr. Gilliam.

Okay. We'll move on to the second question. Here we are product specific. We are specifically concerned are there sufficient data to support an OTC switch of loratadine for CIU or a more general urticaria claim. We're talking specifically about the data we heard about this morning.

What I would like to do here is limit this really just to answer the first part yes or no. Comment if you feel strongly but really the second part of the question is where we'll have an opportunity to talk about specific trials if you think they are indicated.

Let's start on this side of the table, please, Dr. Rosenberg answering just the first part of question 2.

DR. ROSENBERG: Yes.

DR. CANTILENA: Dr. King.

DR. KING: Yes.

DR. CANTILENA: Dr. Clapp.

DR. CLAPP: Yes.

DR. CANTILENA: Excuse me?

DR. D'AGOSTINO: The question is an or question, CIU or more general. What are we responding to?

DR. CANTILENA: Yes, it's actually an or so it's either/or.

Dr. Ganley, do you want the specific as the indication or just either/or?

DR. GANLEY: Well, I think it would be helpful rather than just giving yes or no. There's an over-emphasis on a vote of yes or no and the thoughts are more important.

I think the dermatologists voted they would like a broader claim and by voting yes here they would be stating that they think the company has provided sufficient information for a broader claim. If that's your opinion, that's fine and they don't need to do any other study presumably.

DR. KING: I was voting for a follow-up study so that's different.

DR. ROSENBERG: I misunderstood. I'm sorry.

DR. CANTILENA: I apologize for that. I was actually using that as written as sort of an either/or. As I understand it now, Dr. Ganley, you would like yes or no and an explanation in terms of the specific indication as proposed versus a more general indication. Is that correct? Yes or no for the specific switch for CIU. Yes or no for the general urticaria.

DR. GANLEY: I think --

DR. CANTILENA: Is it yes or no for CIU only, yes or no for general urticaria? We're sort of splitting it into two questions.

DR. TEMPLE: You really already answered the first part of that question. That is, everybody agrees there's enough data for a switch for CIU because --

DR. CANTILENA: No. Actually that was just --

DR. TEMPLE: No.

DR. CANTILENA: -- as modified could it be an OTC indication. Now we are product specific in terms of the data presented.

DR. TEMPLE: Okay.

DR. CANTILENA: The question would be basically split into two questions.

DR. TEMPLE: That's fair. Fine.

DR. CANTILENA: Okay. Let's go ahead and split the question, Dr. Rosenberg. Are there sufficient data to support an OTC switch of loratadine for CIU?

DR. ROSENBERG: Yes.

DR. CANTILENA: Are there sufficient data to support a switch of OTC for a more general urticaria claim?

DR. ROSENBERG: There may be but we haven't seen it here.

DR. CANTILENA: So that would be a no?

DR. ROSENBERG: That would be a no as we didn't ask for it and they didn't bring it. Yes, it would be a no as of this minute.

DR. GANLEY: The answer to question 1 seems like there was a consensus that it should be a broader claim. I'm not sure that it's relevant then. The CIU sounds like that's not what people what to have. The question really should read if your answer to question is yes, is there sufficient data to support an OT switch of loratadine for a more general urticaria claim. Everyone has said that they would like a broader claim.

DR. ROSENBERG: Well, if I'm still voting I would say whether that information -- let's read it exactly. Are there sufficient data? Whether there are or are not I don't think as I sit here to vote I don't know if there are or not.

DR. CANTILENA: But as it is we have amended question 1 to the more generic sense, could CIU be an OTC indication. Answering in the affirmative there and saying that it should be broader. Now question 2 --

DR. GANLEY: Could urticaria be and then you followed it up by saying should it be --

DR. CANTILENA: What I specifically said

before the vote question 2 is product specific. It's actually their data and that's why --

DR. GANLEY: Question 1 was not whether could CIU be a OTC. It was could urticaria be an OTC claim. Then it was followed up with whether it should be CIU or should it be a broader claim.

DR. CANTILENA: Right. But that was not product specific or had anything to do with the data.

DR. GANLEY: No, but if everyone here is saying that they think it should be a broader claim, then if you answer yes, that they have enough information to switch loratadine for a CIU claim, there's something missing there for me.

DR. TEMPLE: Charlie, that's true but I think what Lou is saying is now they are asking -- I mean, whatever your preference might be, maybe you really think a broader claim would be a really great thing, but you still have to ask whether there's a basis for it. The first step in question 2 is to say do they have the data for CIU claim.

Presumably that's what their studies are in but I guess there's other questions. Then the next

part of that is do they have data for a broader claim. The committee may say, "I don't know," or "Yes," or send it back to you to think about or a lot of other things. How does that sound?

DR. CANTILENA: That sounds reasonable. Thank you.

DR. CANTILENA: Jonca.

DR. BULL: One other point of clarification here. Based on the approach you've taken to question 1, which is looking broadly at whether or not it's appropriate to have the OTC indication and you're saying yes to the OTC indication, and yes that it should be the broad one. Is that right? Is that what we want just in terms of conceptually?

DR. CANTILENA: Right.

DR. BULL: Okay.

DR. CANTILENA: In sort of a generic sense.

DR. BULL: On No. 2 where you are more product specific it appears that if you -- the question now is on the data to support the general

claim because you've already agreed that you want to see a general claim. Is it mute for the CIU or general claim or are we going back to that?

DR. ROSENBERG: I think it's what the meaning of "are" are.

DR. CANTILENA: Let's not get into that. Seriously, I think --

DR. BULL: I just want to clarify what groundwork you've laid with question 1 for question 2.

DR. CANTILENA: Question 1 was really in sort of a generic sense. Now question 2 is product specific. In essence we're saying are there data to support CIU as presented as proposed and are there data to also support the more general claim of urticaria. We're trying in essence to go -- if you're comfortable extending the data that they presented for CIU as adequate for the more general claim, then the answer to the second question is yes.

DR. GANLEY: But I think one of the things here is whether we have to make decisions not on a general -- if the committee feels that they -- if they want to see an urticaria claim, they would want to see

a broader claim, then that's the way we should go. If everyone thinks it could be broader but I would accept CIU, that's a different issue because if you answer that you want a broader claim, then that's what we're going to tell not just this company but other companies.

DR. WOOD: Charlie, you're getting yourself into a box because if you follow that down the logical path and the committee votes for a CIU as having data and not having data for the other but they want a broad claim, then that's your interpretation but it would be hard to approve.

DR. GANLEY: Well, no. I think someone -- if you construct, as John has tried to construct, that this and an antihistamine, he's very comfortable and I may be very comfortable with that. There's no additional efficacy studies to look at acute hives to see whether that's a -- you know, you need to do additional efficacy studies because if we've already established it worked in hives, I don't need efficacy studies.

That being said, then, well, if this is a

general claim for hives, what additional information would I want to have? Is it a labeling comprehension study or an actual use study? But to go back and revisit when everyone has come to some understanding that the preference here is whether it should be a broader claim or CIU claim. The issue then comes for the company. Do they have information to support a broader claim here.

DR. TEMPLE: But, Charlie, that's the question.

DR. D'AGOSTINO: But what if you don't accept our response to 1? Then you don't want to know about if we were hemmed into CIU in 2 to give a response?

When you have deliberations, you say in the broader claim we don't like at all what the committee said so we're chucking out their response to 1. We go to 2 and we're only responding to a broader claim so we haven't given you much information. I think it would be nice for us to do the two pieces.

DR. TEMPLE: Yeah, but 1 was the statement about what you hoped there were data support. It

wasn't a statement that there were data support. That comes later. We understand, I think, because it's going to be used anyway and various other reasons, you would like to see it labeled for urticaria as a more general matter.

But this question was, as you're understanding it, are there data that support a claim in CIU only if that were the best we could do, or is there good reason to extrapolate the information from that use to a more general statement about urticaria on which you're going to give a separate opinion. Part of it may be that we have to go think about that some more. We don't know yet.

DR. CANTILENA: Okay. So let me just rephrase this. This was supposed to be the easy part. All right. We basically agreed to split this question to answer it basically separately for the indications. Are there sufficient data to support an OTC switch of loratadine for CIU? The first part.

Second part: Are there sufficient data to support an OTC switch of loratadine for a more general urticaria claim? Product specific, the information

that we heard this morning and it's in our packets.

So far we've had Dr. Rosenberg, I believe, vote yes for CIU and no for the more general claim. Is that correct?

DR. ROSENBERG: Yes.

DR. CANTILENA: Okay.

Dr. King.

DR. KING: Same response. I think in terms of the specific agent they did provide the data. I don't think the data is here about the general thing. I would like to see that as a goal. I think they would come forward with that and it would be coupled with a use study to find out when this is released, if that's true, after the fact.

I think they didn't present the data because they probably weren't thinking they were going to have to do that. I think this group just haven't seen that data.

DR. CANTILENA: Okay. Dr. Clapp.

DR. CLAPP: Yes for the switch for CIU but no for the general claim. My concern is based on the efficacy in children. Although we presume based on

what the dermatologists have said that the mechanism for urticaria is the same regardless to the acute versus chronic idiopathic as being the same, I still don't have the sense of certainty that in children the efficacy is the same in the acute circumstance. I would like to see some data to confirm that reality.

DR. CANTILENA: Thank you.

Dr. Williams.

DR. WILLIAMS: Yes to the first part and no to the second part. I believe the sponsor should have that type of information in the years of usage that they've had already so I don't think it should be too difficult for them to produce it.

DR. CANTILENA: Thank you.

Dr. Wood.

DR. WOOD: Yes to the first part and to the second part I would defer to the FDA looking at the data that I suspect is in the literature to make that decision on the acute. From what we have from Dr. Rosenberg it sounds like that data is already out there.

DR. CANTILENA: So based on the

information that was presented it would be a no. But if there was sufficient information available in the file or in the literature, then it would be a yes.

DR. WOOD: I'm precise. Are there sufficient data to support an OTC switch for a more general claim. The answer to that is I don't know that we can answer that question because we haven't had that data presented. However, the answer might be yes or no and that's why I'm saying defer it for further review to the FDA. To say that there are not data I don't think anyone can answer that.

DR. CANTILENA: Okay.

Dr. Sachs.

DR. SACHS: I would say yes to the CIU with the one caveat I think the data presented only went down to age 12, and no to the general indication because I think we need the actual use studies as I've said before.

DR. CANTILENA: Dr. Davidoff.

DR. DAVIDOFF: I would say yes to the CIU question and to the more general claim, I would say no, that the data at least have not be presented to us

here. I think it's not just efficacy data which I think are probably going to be pretty easy to come by.

I would be rather more concerned about safety data. I think anaphylaxis is essentially not an issue for CIU but it is potentially for acute urticaria. I think they are rather different situations and we would need more information on that.

DR. CANTILENA: Thank you.

Dr. Lam.

DR. LAM: Yes to the first one and to the second one, I don't know where there is data out there and, therefore, I can't really make a decision whether it's sufficient or not.

DR. CANTILENA: So you're voting like Dr. Wood on the second part.

Dr. Johnson.

DR. JOHNSON: Yes to the CIU and, like many around the table, for the more general clearly the data weren't presented. They may be out there somewhere. I'm not convinced that further trials are necessary but I think we need more information.

DR. CANTILENA: Dr. Uden. Hold on one

second.

Dr. Johnson, so you're voting as Dr. Lam and Dr. Wood. You're not sure about the second part. It's not a yes or no.

Dr. Uden.

DR. UDEN: Yes for the first part and the second part I'm a Wood, Lam, Johnson believer.

DR. CANTILENA: Dr. Krenzelok.

DR. KRENZELOK: I vote yes for the first part and my dimpled chad on part 2 will be that I'll vote no until there are more data to change that vote.

DR. CANTILENA: Thank you.

Dr. D'Agostino.

DR. D'AGOSTINO: I vote yes on the first part, but I want to emphasize that I was quite serious about the response to question 1. I don't think that -- I think this is much too narrow. I think they have the data but it's much too narrow an indication for an OTC.

On the second part I'm going to say no because I haven't seen the data. The data may be there but I'll say no for the data that I've seen and

later we'll talk about is there control clinical trial data on the literature. There's a lot of data in where it has already been approved for OTC use.

They should be able to collect data there on at least the safety issues and other data sources which would help in terms of whether or not there is enough data out there for approval. Right now I haven't seen it so I vote no.

DR. CANTILENA: Dr. Szefler.

DR. SZEFLER: I haven't seen the specific data for either indication other than the publications that were included in the material we got so I'm going to say yes to the first part presuming there was adequate data there to get it approved as an Rx indication and defer to the FDA for that decision and it's already been made.

The second category really depends on whether you accept chronic urticaria as a model for urticaria in general. The FDA had said no to that. Either there has to be data in the specific disease in terms of acute urticaria or there has to be a reexamination of the similarities between chronic

urticaria and general urticaria.

I think if they could settle on accepting that as common mechanisms and as this being a palliative drug, then I would go along with extending on current data. Otherwise there's a need for additional data. It would be essentially exactly what Dr. Wood said.

DR. CANTILENA: Dr. Joad.

DR. JOAD: Yes to the first one and no to the second one. I do think there needs to be a good solid clinical trial in acute urticaria. I would also like to add that special emphasis should be done on the product label informing people about what to look for for anaphylaxis and getting emergency help right away.

I think there were some concerns with the sponsors. Results were there were a lot of the people would talk to their doctor and it was not very clear that they would recognize it as an emergency. A lot of work on the product label about recognizing anaphylaxis as an emergency.

DR. CANTILENA: Thank you.

Dr. Dykewicz.

DR. DYKEWICZ: Yes for CIU. No for general at this time.

DR. CANTILENA: Okay. Comments from Dr. Alfano?

DR. ALFANO: A couple comments. One, I guess we see why the sponsor submitted for CIU as the day plays itself out. Two, I wonder if we would have voted differently if instead of we asked the question is there sufficient data we ask is there sufficient basis to support a more general claim because we heard some erudite physicians talk about the physiology of this as being the same, and yet there was no data so there could be a semantic witch haunting us as we made these decisions.

I guess the final comments would be you know if we don't move this, then we will deal with the status quo which is less safe products on the market used in the fashion that they are for these conditions anyway without the warning label for anaphylaxis. I guess the question is will be have left the world a better place.

DR. CANTILENA: Okay. Thank you. My vote is for the first part, yes, and the second part for the general claim, no.

Before we get to the other types of data that are needed for this second part, just an announcement. Dr. Hoff has an emergency phone call at the registration desk outside. It's just outside the door and to your left is the registration desk if you would take care of that.

Okay. Question No. 2. Here I would actually like not to talk about the label that they proposed specifically, but I would like to advise the sponsor and FDA here what other types of data are needed such as clinical trials for efficacy, safety, label comprehension or actual use.

Since I believe everyone answered in the affirmative for CIU, then we are really just left with those who answered negatively for the more general urticaria claim.

What I would like to do is actually, if you want to, just volunteer what specific kind of studies you would like to see to support the more

general claim, I think we would do that as opposed to going around the room we'll just open it up for a minute. Also, if you voted you don't know or you're not sure because you haven't seen it, you can also comment as well.

Dr. Rosenberg.

DR. ROSENBERG: I think a conscientious literature search such as used for medianalysis.

DR. CANTILENA: Thank you.

Dr. Sachs.

DR. SACHS: I am sure, as alluded to, that data exist on drug/drug interactions or the absence of them in these products if that would be helpful information, the poison control data, and the actual use studies in kids as well as adults if you're going to go down to six.

DR. CANTILENA: Other types of study recommendations, Dr. Krenzelok?

DR. KRENZELOK: I'm sorry. I was going to make a comment about a label. Is that okay or do you want to wait on that?

DR. CANTILENA: If we can cover that on

No. 3 unless it's a comment about a label comprehension study.

Dr. Wood.

DR. WOOD: I think without sounding factious we should have studies that actually determine whether people understand chronic idiopathic urticaria better than hives and really focus on what vocabulary people really use.

The other types of data that are needed such as clinical trials for efficacy, etc., I think most of that data is already out there, at least from what Dr. Rosenberg days. I think it's just a question of reanalyzing it and resurfacing it. I'm not sure that we need to leave the impression that major new clinical trials are needed.

DR. CANTILENA: Dr. D'Agostino.

DR. D'AGOSTINO: Do we think there are clinical trials on Claritin in acute hives? I mean, when we say there's data out there, clinical trial data, we're talking about just the whole class of antihistamines that we can extrapolate to this?

DR. WOOD: I think the answer is we don't

know. We've not had that presented and, therefore, it would be foolish to comment on whether that exist or not, except to say that the dermatologists, Dr. Rosenberg specifically, said there were class A evidence to support use of antihistamines.

DR. D'AGOSTINO: The old line antihistamines? These antihistamines? Just so I'm --

DR. WOOD: Non-sedating.

DR. ROSENBERG: Non-sedating antihistamine was given that citation. I mean, I didn't read the -- I didn't do a search for that.

DR. D'AGOSTINO: Right. None of us have.

DR. CANTILENA: So your question is are there studies that use this drug for acute hives? Is that your question?

DR. D'AGOSTINO: Well, we've -- exactly. We've said CIU was -- we believe the acute part is left hanging.

DR. CANTILENA: Dr. Clayton, are there studies using loratadine for acute hives?

DR. CLAYTON: Not that I'm aware of.

DR. CANTILENA: Okay. So they are not

available.

Any other comments about studies? Dr. Davidoff.

DR. DAVIDOFF: Well, just to get back to the point about studying safety versus studying efficacy. Obviously studying safety is much more difficult, essentially impossible to do in the broad sense in a controlled trial of any manageable size.

I think safety is a big part of the issue here so I would think the kind of data that would be needed for convincing information about safety would include a variety of possible approaches.

Other people know them better than I, but post-marketing surveillance clearly would be one of them, retrospective looks, better or deeper looks into existing data and so on. I think that distinction has to be made because I think the efficacy data will not be so difficult to get.

DR. CANTILENA: Yes, Dr. D'Agostino.

DR. D'AGOSTINO: Where -- in the countries where this has been approved OTC, do they collect safety data? Do you feel comfortable there will be

safety data from those countries?

DR. CANTILENA: Dr. Ganley or Katz, Temple?

DR. KATZ: They do collect safety data but you run into the same problem.

DR. D'AGOSTINO: Spontaneous.

DR. KATZ: That's right. Spontaneous reports so that you have no denominator. As a result, certain countries are better than others at getting data but you're not quite sure when you try to put into perspective what it really means because, again, there's no denominator.

DR. CANTILENA: Dr. Temple.

DR. TEMPLE: We're talking about events that must be unbelievably rare so your denominator is not usually a problem on something like this. I think you want to know whether there are really any people who didn't go get their anaphylaxis treated because they were using an over-the-counter non-sedating antihistamine. Like most spontaneous reporting, the denominator is your whole country. You can't do better. You can't do a study of --

DR. D'AGOSTINO: So if the spontaneous reporting good, then it counts.

DR. TEMPLE: In the UK it's thought to be pretty good. In Canada it's thought to be pretty good so those aren't so bad. You're not going to do a study of 2,000 people and find --

DR. D'AGOSTINO: No, no. The question is we're talking about safety data and one possibility is, what do they say, 10 years of history?

DR. TEMPLE: Sure. That can be looked at.

DR. WOOD: But, Bob, you're absolutely right. These are data that are going to be readily available. Anaphylaxis is not something that doesn't get spotted.

DR. TEMPLE: Yeah. One of my questions is what kind of anaphylaxis gets reported. For example, if it doesn't seem to be related to a drug, it probably wouldn't be reported to Medwatch.

DR. WOOD: No, but it's going to be a death certificate data.

DR. TEMPLE: I don't think we know yet how good it's going to be but that's what there's going to

be. There's isn't really going to be anything else. You can't do a study of this. There can't be a lot of them.

DR. JOAD: That was going to be my point. I'm not sure it would be reported as an adverse drug event because no one would think that the anaphylaxis was due to the antihistamine but it certainly could be related to delay in treatment.

I don't know how you would find that from spontaneous reporting. I mean, if there's a way to do it, if we approve this, we should try to figure out a way to do it in the future for post-marketing research.

DR. D'AGOSTINO: We are saying there's data out there and it doesn't sound like we are offering much by way of what data is and where they can get it. Am I right?

DR. DYKEWICZ: If I can ask maybe Dr. Lee with the SAE data that you had discussed earlier with the 12 percent incidence of anaphylaxis of people who had been on loratadine when there is a prior history of urticaria, would that have enough detail in that

database to see whether, for instance, there had been, I don't know, some effort to use loratadine during an anaphylic event?

DR. LEE: Yes. Some of that data was pretty detailed. I mean, there are individual case reports. The case report that I mentioned of the Canadian woman who took -- was the only anaphylaxis death in the database.

Some of these reports are detailed enough to be able to get a feel as to whether or not the event in some circumstances what the order of -- what happened was, when the drug was taken. Was it taken after the patient had symptoms. In some cases not.

DR. CANTILENA: Okay. I think there was a comment over here. Dr. Uden and then Dr. Davidoff. Do you still have a comment?

MS. ROHANE: Excuse me. Do you need any more information about the cases on anaphylaxis in the post-marketing safety database? What I can tell you is that within the entire marketing of loratadine there have been 20 reported with the plain tablet.

Of those 20 four were in patients who took

the drug with a CIU diagnosis. Of the four there was one in Canada who took the drug for acute urticaria. The other 16 were in other diagnoses including allergic rhinitis, sinusitis unspecified. There's a variety of other things.

DR. SACHS: But do you have information on whether taking loratadine, for example, delayed their treatment? That's kind of the question we're asking.

MS. ROHANE: Well, the issue there is that this all comes from post-marketing safety surveillance. Some cases have very little information and others have much more detail. It depends on the case.

DR. CANTILENA: Okay. Dr. Davidoff.

DR. DAVIDOFF: Well, I agree here's detail and you need to look at the detail of the case. There's no other way to get the kind of information you'll need because it's not going to be reported as an adverse affect in the usual sense.

DR. CANTILENA: Dr. Uden.

DR. UDEN: I haven't heard it explicitly stated in this round but assuming that there's going

to be a more general indication and assuming that might be hives, that we do have them redo label comprehension study that adequately represents the diversity of the United States and the literacy of the United States again. Make sure that they do something with a new label.

DR. CANTILENA: I would second that, Dr. Ganley. I think it's a critical piece of the information package is to make sure that we are effectively communicating in the drug label and if you're going to change the drug label now to a more general indication, I think that has to be tested vigorously. I would agree with Dr. Uden that subpopulations have to be adequately represented.

Anymore comments regarding additional studies for the more general claim?

Dr. Wood.

DR. WOOD: I just want to make a general point, and that is maybe we're all getting tired but we seem to have developed a sort of negative tone about it which I think would be unfortunate because it seems to me that the sponsor came in with an

application for CIU and the committee, or the agency, has taken the position that maybe it should be a broadened indication.

Now they are sort of getting attacked for a broader indication they didn't actually ask for in the first place. I think it's important for us to at least convey to the agency that the sense I get from the committee is there's a broad consensus for a positive view on the CIU indication and this sort of other issue which has been raised is kind of distracting us. I have a sense of unfair play in some ways on that.

DR. CANTILENA: Well, I'm not sure if it's unfair or if we are actually anticipating sort of the next move and we're trying to help out on both sides. It was actually our group that I think stimulated the discussion for the more general claim. I understand your point and it's well taken.

DR. D'AGOSTINO: I thought I was following your lead, Dr. Wood, in going to hives and so forth.

DR. WOOD: I still hives is the right way to go.

DR. D'AGOSTINO: Can I --

DR. CANTILENA: Yes.

DR. D'AGOSTINO: If in the search for data, safety, and efficacy it doesn't materialize, the safety issues sound very profound and maybe there is enough from the company's spontaneous reporting or whatever that they do for adverse events.

What is our sense about the efficacy? I mean, how much would be push on the efficacy part if it turns out that the literature isn't convincing enough. Do we feel that they must put together a clinical trial? Is there no extrapolation?

DR. WOOD: Well, I think if there was no data on the efficacy -- you mean in acute hives?

DR. D'AGOSTINO: In acute, yes.

DR. WOOD: Then I would return to the original suggestion I made, that the indication should be hives that has been diagnosed by a physician which would be compatible with the CIU indication but, it seems to me at least, more understandable to the average patient than over the counter.

DR. CANTILENA: Yeah. I think Dr. Temple

sort of explained the situation as far as how the agency would have to sort of go by the law if there are no data for that as a specific indication.

DR. D'AGOSTINO: Well, we said in No. 1 that we think it should be broader and now I'm asking if the broader data is not there, there's one way of getting a good positive response by saying then put after you've seen your physician and that doesn't compel the company and the FDA and the advisory committees that you must have efficacy data and, therefore, you must have a clinical trial.

DR. CANTILENA: Okay. Any other comments about additional studies before we answer the last question?

Dr. Sachs.

DR. SACHS: It was raised. I just want to make sure you do note about the patient's ability to recognize hives themselves. You may roll your eyes but let me just point out that take a TB skin test. They did a study on whether patients could self-read whether a TB skin test was positive or negative and they could not.

I think you do have to at least look at it, you know, could you distinguish the dangerous things like purpura from hives. It may not matter if you can't tell a mosquito bite from a hive but purpura from a hive you probably need to know.

DR. CANTILENA: Okay. Since we've split up question 2, question 3 basically has to refer to the indication of CIU which everyone answered yes to. Now as we are referring specifically to CIU, what are your recommendations for appropriate labeling of loratadine with regard to indications, warnings, and directions for CIU because that's what we answered in the affirmative.

Just so we are guaranteed to get everyone's input and to keep everybody awake, why don't we start with Dr. Alfano and just go around the table with specific recommendations for CIU.

DR. ALFANO: I just urge the sponsor to make sure they have maximized the warning of the consumer for anaphylaxis so they know to seek care.

DR. CANTILENA: Thank you.

Dr. Dykewicz.

DR. DYKEWICZ: Well, I'm a little bit torn by the stricture not to go beyond the CIU indication. I think even in a situation where CIU has been diagnosed by a physician, one has to be mindful that there could be evolution to a vasculated process, for instance.

I think that would be something about purpuric however that would be found in a label comprehension study or in a use study to indicate that change in skin color at the site or a purple lesion, those would be reasons to seek medical attention or something.

DR. CANTILENA: Thank you.

Dr. Joad.

DR. JOAD: For the CIU indication I don't have any additional comments.

DR. CANTILENA: Dr. Szefler for CIU.

DR. SZEFLER: I think a clear definition. I think as Dr. Wood mentioned a number of times now, I don't think the public is aware of what chronic idiopathic urticaria means. We often just call it chronic hives or recurrent hives.

I think a clear definition with some warnings about when it extends beyond or went to see a physician presumably again would be indicated. I don't know if package inserts have actual pictures of what a hive looks like but if that could be done, it would be help so they could kind of understand what we're talking about.

DR. CANTILENA: Dr. D'Agostino.

DR. D'AGOSTINO: I don't have anything to add.

DR. CANTILENA: Dr. Krenzelok.

DR. KRENZELOK: Thank you. Dr. Wood and Dr. King expressed some very simplistic things about how people in Tennessee perceive words and so on. I think that is really good. I think we really need to downplay this chronic urticaria business.

Dr. Ferguson in his presentation emphasized unexplained hives that keep coming back. Well, there might be a better way to say that but that is actually fairly simplistic and I think we need to present it to the public that way.

Then Dr. Wilkin in slide 42 had some

excellent patient admonitions about when the patient needs to contact a physician. I think those should really be included on the outside of the package label or inside. Somewhere to warn the patient accordingly. Thank you.

DR. CANTILENA: Dr. Joad, did you have something else?

DR. JOAD: I just to make a comment about the idiopathic or unexplained. My understanding from the reading is that in 40 percent of the cases we do have an explanation. It's the IGG against the IGE receptor or the IGE. I realize historically we haven't known but we do know. That's a complication, too. There sounds like there is a disease out there that does have a pathophysiology that explains everything.

DR. CANTILENA: Dr. Uden.

DR. UDEN: I have a question. Maybe the sponsor can answer this. We handed around one of the suggested labels prior to what our discussion was. Was there anything -- this isn't related to urticaria.

Was there anything in there about

sedation? They call it non-drowsy. Was there anything about sedation as one of the side effects? I know your advertisements say may cause drowsiness so this is a clarification for me.

DR. CLAYTON: (Off microphone.)

DR. UDEN: Because -- well, this is a bigger issue and it's not related to this so maybe I should just shut up. I mean, the non-sedative antihistamines are less sedative. I just wanted to know if "may cause drowsiness" is actually in their label even though they call it non-drowsy.

DR. CANTILENA: It's on the ads.

DR. UDEN: It's on the ads, you know, "This may cause drowsiness." I just wanted to have truth in label language and non-drowsy is not truth in labeling.

DR. CANTILENA: Dr. Johnson.

DR. CLAYTON: (Off microphone.)

DR. CANTILENA: Dr. Clayton, could you use a microphone, please? We're having a hard time hearing.

DR. CLAYTON: I had given an incomplete

thought to Dr. Uden's comment. You mentioned the advertising for non-sedating antihistamines. I'm talking specifically about loratadine, the advertising just mentioned as the primary side effect but no greater than placebo in the clinical trials.

DR. CANTILENA: Dr. Johnson.

DR. JOHNSON: My recommendations are related to the packaging. I think I have concern about this with a lot of OTC products. A lot of OTC products are packaged in blister packs. I suspect what happens is people might read the box when they purchase it. They go home and open it up and they probably throw away the package insert.

They throw away the box, and what they have left is a blister pack which on the back has the name of the drug and the dose. One thing that I might suggest is that there is consideration to give in to not marketing these in blister packs but in bottles where you could at least put critical warning information and it's always there.

As long as the patient has tablets left they always have the information. Whereas I think in

blister packs in most situations they are going to lose that information as soon as they purchase the product.

DR. CANTILENA: Thank you.

Dr. Lam.

DR. LAM: I like the information that Dr. Wilkin has suggested, although I'm not really sure now we can fit all that information into one tiny label.

DR. CANTILENA: Okay. Dr. Davidoff.

DR. DAVIDOFF: Yes. I would certainly support the emphasis on hives rather than chronic idiopathic urticaria, although I don't think it hurts to put the longer term in because some doctors will have used that with their patients.

On the safety issue, even though it's not clear the extent to which anaphylaxis is more common, or if it's more common in CIU, it seems to me that it probably isn't less common in CIU than the rest of the population so you may, in fact, still be at risk to develop anaphylaxis and that does certainly provide a rationale for including information, more specific information on when to recognize something more

serious is happening.

DR. CANTILENA: Dr. Gilliam.

DR. GILLIAM: Yeah. Just along this same line. There was a list that somebody had of 10 points of when you should consult your physician or provider, the peanut or latex allergy greater than six weeks, skin bruising or skin tone changes, blistering, and so forth. There were 10 of these points and I think they should be in there.

DR. CANTILENA: On the box or in the package or either?

DR. GILLIAM: I would say definitely on the box. We all know that most people don't read the package inserts so definitely on the box

DR. CANTILENA: Okay. Thank you.

Dr. Sachs.

DR. SACHS: I like the idea of having pictures. Perhaps a do not use type thing. You guys use a lot of color. I don't recall if the warnings said anything about alcohol which probably should be and something about the days of treatment. How are these going to be packaged like a package of seven,

package of 21, package of whatever.

I think that would be useful information for the future. Perhaps a warning to call 911 -- I apologize if I lifted that from anyone over there -- in case of anaphylaxis or respiratory difficulty. Not just a statement to consult your doctor but perhaps call 911.

DR. CANTILENA: Dr. Wood.

DR. WOOD: I don't know what I can add except to say you've got to be careful not to overstuff the label with so many warnings that it becomes incomprehensible to the patient. I think it would be very important in this setting to really try and prioritize what the major issues are and not get it so filled with other things that it becomes actually incomprehensible to a patient which I think we do sometimes.

DR. CANTILENA: Dr. Williams.

MR. JACKSON: My concern is to make sure that they read and follow the directions as indicated on the package. Many of these medications are three times a day or four times a day. We usually don't

have that in the information on the package that this is just a once a day pill.

DR. CANTILENA: Dr. Clapp.

DR. CLAPP: Ditto to what has been said.

DR. D'AGOSTINO: Dr. King.

DR. KING: I'm concerned, again in the Tennessee phrase, about how much they are going to be able to comprehend. I would like to see that there be follow-up studies or preliminary studies on truth in labeling so that we look at and see what you are talking about and do what you're supposed to like once a day or whatever and avoid whatever things you say, you need to go to the physician or whatever.

I don't know about getting 10 indications but I think it's up to the sponsors and the FDA to decide what's going to be the best indication for labeling on the outside of the box to find out if it's going to be used effectively.

DR. CANTILENA: Dr. Rosenberg.

DR. ROSENBERG: I think if the indication will be chronic idiopathic urticaria it has to be -- then you have been seen previously by a doctor who

told you there was no known cause or he didn't know the cause at that time and it should be treated symptomatically.

I think it relieves the symptoms rather than cures. That would be one thing. If it did not have the CIU claim, if, in fact, it were to achieve the broader urticaria claim, then I think we could take out "see your doctor first."

I would think about it in the same way we think about analgesics for headaches for people who could have a brain tumor or laxatives for people who could have cancer and so forth and have the kind of material that John Clayton mentioned, things to look out for and the kind of statement that if it doesn't get better, go see somebody.

But, in addition, because of the anaphylaxis piece, I think it could have a special box or so that says sometimes like this is a symptom of a very serious condition that can strike suddenly and if you think you're having that, really dial 911. It is hard to write those things and get them in little boxes but there are specialist at that.

DR. CANTILENA: Okay. Thank you.

Dr. Ganley, would you like any additional comments about the labeling for the more general claim or have you had about all the advice you can take for one day?

DR. GANLEY: I just want to make one final note. This is the last formal meeting for Dr. Gilliam, Krenzelok, Sachs, and Dr. Neal who is not here today. We appreciate their efforts over the last years and we may look forward to having you back in the future sometime. Thank you.

DR. CANTILENA: Yes. Thank you. Let's give them a round of applause for their endurance.

Are there any other issues from FDA's side or from the sponsor's side that you would like our streamlined advice about?

DR. D'AGOSTINO: What time is it tomorrow morning?

DR. CANTILENA: Tomorrow morning is --

DR. TITUS: Tomorrow morning starts at 9:00 and we are across the room right across the hallway in a smaller room. If you come in here,

you'll be in the wrong meeting.

DR. CANTILENA: Okay. So the closed session for the NDAC is tomorrow at 9:00. Thank you very much everyone.

(Whereupon, at 5:03 p.m. the meeting was adjourned.)